

**WO0031063**

Publication Title:

SUBSTITUTED PYRAZOLES AS p38 KINASE INHIBITORS

Abstract:

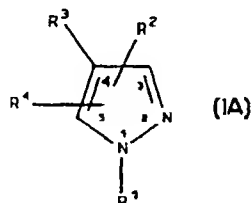
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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification <sup>7</sup> :</p> <p>C07D 401/04, A61K 31/415, 31/47, 31/445, 31/44, 31/50, 31/505, 31/52, C07D 405/14, 401/14, 409/14, 403/04, 487/04, 473/00, 413/14, 417/14, 471/04, A61P 29/00 // (C07D 487/04, 293:00, 231:00) (C07D 471/04, 221:00, 209:00)</p>	<p>A1</p>	<p>(11) International Publication Number: <b>WO 00/31063</b></p> <p>(43) International Publication Date: 2 June 2000 (02.06.00)</p>
<p>(21) International Application Number: PCT/US99/26007</p> <p>(22) International Filing Date: 17 November 1999 (17.11.99)</p> <p>(30) Priority Data: 09/196,623                      20 November 1998 (20.11.98)      US</p> <p>(71) Applicant (<i>for all designated States except US</i>): G.D. SEARLE &amp; CO. [US/US]; Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (<i>for US only</i>): ANANTANARAYAN, Ashok [US/US]; 54 Lisk Drive, Hainesville, IL 60030 (US). CLARE, Michael [GB/US]; 5154 West Brown Street, Skokie, IL 60077 (US). COLLINS, Paul, W. [US/US]; 2317 Carillon Drive, Grayslake, IL 60030 (US). CRICH, Joyce, Z. [US/US]; 1501 G. Topp Lane, Glenview, IL 60025 (US). DEVRAJ, Rajesh [IN/US]; 1331 Oak Borough Drive, Ballwin, MO 63021 (US). FLYNN, Daniel, L. [US/US]; One Amgen Center Drive, Thousand Oaks, CA 91320 (US). GENG, Lifeng [CN/US]; 5300 Davis Street, Skokie, IL 60077 (US). GRANETO, Matthew, J. [US/US]; 352 Hartwell Court, Chesterfield, MO 63017 (US). HANAU, Cathleen, E. [US/US]; 15551 Wendimill Drive, Chesterfield, MO 63017 (US). HANSON, Gunnar, J. [US/US]; 7410 Keystone Avenue, Skokie, IL 60077 (US). HARTMANN, Susan, J. [US/US]; 613 West Essex Avenue, Kirkwood, MO 63122 (US). HEPPELLE, Michael [DE/US]; 1460 Keystone Court, St. Charles, MO 63303 (US). HUANG, He [CN/US]; 2309F S. Stewart Avenue, Chicago, IL 60616 (US). KHANNA, Ish, K. [CN/US]; 1821 S. Falcon Drive, Libertyville, IL 60048 (US). KOSZYK, Francis, J. [US/US]; 11 Wildwood Drive South, Prospect Heights,</p>		<p>IL 60070 (US). LIAO, Shuyuan [US/US]; 1536 Walters Avenue, Northbrook, IL 60062 (US). METZ, Suzanne [US/US]; 525 Westernmill Drive, Chesterfield, MO 63017 (US). PARTIS, Richard, A. [US/US]; 2221 Noyes Street, Evanston, IL 60201 (US). PERRY, Thao, D. [US/US]; 516 Bloom Street, Red Bud, IL 62278 (US). RAO, Shashidhar, N. [IN/US]; 736 Bellerive Manor Drive, St. Louis, MO 63141 (US). SELNESS, Shaun, Raj [US/US]; 1875 Cedarmill Drive, Chesterfield, MO 63017 (US). SOUTH, Michael, S. [US/US]; 11671 Cheiftain Drive, Chesterfield, MO 63146 (US). STEALEY, Michael, A. [US/US]; 502 Juniper Parkway, Libertyville, IL 60048 (US). TALLEY, John, Jeffrey [US/US]; 4701 Clifton Avenue, St. Louis, MO 63109 (US). VAZQUEZ, Michael, L. [US/US]; 614 Castle Meadows Court, Ballwin, MO 63021 (US). WEIER, Richard, M. [US/US]; 240 Hickory Court, Lake Bluff, IL 60044 (US). XU, Xiangdong [CN/US]; 7498 Abbey Road, Gurnee, IL 60031 (US). YU, Yi [CN/US]; 9065 Grosse Point Road, Skokie, IL 60077 (US).</p> <p>(74) Agents: SCRIVNER, Alan, L. et al.; G.D. Searle &amp; Co., Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US).</p> <p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>

(54) Title: SUBSTITUTED PYRAZOLES AS p38 KINASE INHIBITORS



(57) Abstract

A class of pyrazole derivatives is described for use in treating p38 kinase mediated disorders. Compounds of particular interest are defined by Formula (IA), wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are as described in the specification.

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**SUBSTITUTED PYRAZOLES AS p38 KINASE INHIBITORS****Cross-Reference to Related Applications**

5           This application is related to U.S. Provisional Application Serial No. 60/047,570 filed May 22, 1997 and U.S. Application Serial No. 09/083,670 filed May 22, 1998.

10   **Field of the Invention**

          This invention relates to a novel group of pyrazole compounds, compositions and methods for treating p38 kinase mediated disorders.

15   **Background of the Invention**

          Mitogen-activated protein kinases (MAP) is a family of proline-directed serine/threonine kinases that activate their substrates by dual phosphorylation. The kinases are activated by a variety of signals including nutritional and osmotic stress, UV light, growth factors, endotoxin and inflammatory cytokines. The p38 MAP kinase group is a MAP family of various isoforms, including p38 $\alpha$ , p38 $\beta$  and p38 $\gamma$ , and is responsible for phosphorylating and activating transcription factors (e.g. ATF2, CHOP and MEF2C) as well as other kinases (e.g. MAPKAP-2 and MAPKAP-3). The p38 isoforms are activated by bacterial lipopolysaccharide, physical and chemical stress and by pro-inflammatory cytokines, including tumor necrosis factor (TNF- $\alpha$ ) and interleukin-1 (IL-1). The products of the p38 phosphorylation mediate the production of inflammatory cytokines, including TNF and IL-1, and cyclooxygenase-2.

          TNF- $\alpha$  is a cytokine produced primarily by activated monocytes and macrophages. Excessive or unregulated TNF production has been implicated in mediating a number of diseases. Recent studies indicate that TNF has a



causative role in the pathogenesis of rheumatoid arthritis. Additional studies demonstrate that inhibition of TNF has broad application in the treatment of inflammation, inflammatory bowel disease, multiple sclerosis and asthma.

TNF has also been implicated in viral infections, such as HIV, influenza virus, and herpes virus including herpes simplex virus type-1 (HSV-1), herpes simplex virus type-2 (HSV-2), cytomegalovirus (CMV), varicella-zoster virus (VZV), Epstein-Barr virus, human herpesvirus-6 (HHV-6), human herpesvirus-7 (HHV-7), human herpesvirus-8 (HHV-8), pseudorabies and rhinotracheitis, among others.

IL-8 is another pro-inflammatory cytokine, which is produced by mononuclear cells, fibroblasts, endothelial cells, and keratinocytes, and is associated with conditions including inflammation.

IL-1 is produced by activated monocytes and macrophages and is involved in the inflammatory response. IL-1 plays a role in many pathophysiological responses including rheumatoid arthritis, fever and reduction of bone resorption.

TNF, IL-1 and IL-8 affect a wide variety of cells and tissues and are important inflammatory mediators of a wide variety of disease states and conditions. The inhibition of these cytokines by inhibition of the p38 kinase is of benefit in controlling, reducing and alleviating many of these disease states.

Various pyrazoles have previously been described. U.S. Patent No. 4,000,281, to Beiler and Binon, describes 4,5-aryl/heteroaryl substituted pyrazoles with antiviral activity against both RNA and DNA viruses such as myxoviruses, adenoviruses, rhinoviruses, and various viruses of the herpes group. WO 92/19615, published November 12, 1992, describes pyrazoles as novel fungicides. U. S. Patent No. 3,984,431, to Cueremy and Renault, describes derivatives of pyrazole-5-acetic acid

as having anti-inflammatory activity. Specifically, [1-isobutyl-3,4-diphenyl-1H-pyrazol-5-yl]acetic acid is described. U. S. Patent No. 3,245,093 to Hinsgen et al, describes a process for preparing pyrazoles. WO  
5 83/00330, published February 3, 1983, describes a new process for the preparation of diphenyl-3,4-methyl-5-pyrazole derivatives. WO 95/06036, published March 2, 1995, describes a process for preparing pyrazole derivatives. US patent 5,589,439, to T. Goto, et al.,  
10 describes tetrazole derivatives and their use as herbicides. EP 515,041 describes pyrimidyl substituted pyrazole derivatives as novel agricultural fungicides. Japanese Patent 4,145,081 describes pyrazolecarboxylic acid derivatives as herbicides. Japanese Patent  
15 5,345,772 describes novel pyrazole derivatives as inhibiting acetylcholinesterase.

Pyrazoles have been described for use in the treatment of inflammation. Japanese Patent 5,017,470 describes synthesis of pyrazole derivatives as anti-  
20 inflammatory, anti-rheumatic, anti-bacterial and anti-viral drugs. EP 115640, published Dec 30, 1983, describes 4-imidazolyl-pyrazole derivatives as inhibitors of thromboxane synthesis. 3-(4-Isopropyl-1-methylcyclohex-1-yl)-4-(imidazol-1-yl)-1H-pyrazole is  
25 specifically described. WO 97/01551, published Jan 16, 1997, describes pyrazole compounds as adenosine antagonists. 4-(3-Oxo-2,3-dihydropyridazin-6-yl)-3-phenylpyrazole is specifically described. U.S. Patent No. 5,134,142, to Matsuo et al. describes 1,5-diaryl  
30 pyrazoles as having anti-inflammatory activity.

U.S. Patent No. 5,559,137 to Adams et al, describes novel pyrazoles (1,3,4,-substituted) as inhibitors of cytokines used in the treatment of cytokine diseases. Specifically, 3-(4-fluorophenyl)-1-(4-  
35 methylsulfinylphenyl)-4-(4-pyridyl)-5H-pyrazole is described. WO 96/03385, published February 8, 1996,

describes 3,4-substituted pyrazoles, as having anti-

inflammatory activity. Specifically, 3-methylsulfonylphenyl-4-aryl-pyrazoles and 3-

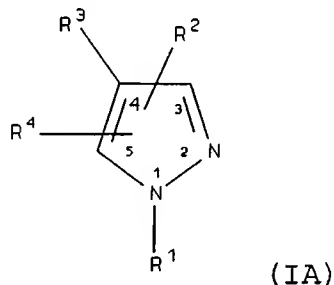
5 aminosulfonylphenyl-4-aryl-pyrazoles are described.

Laszlo et al., Bioorg. Med. Chem. Letters, 8 (1998) 2689-2694, describes certain furans, pyrroles and pyrazolones, particularly 3-pyridyl-2,5-diaryl-pyrroles, as inhibitors of p38 kinase.

10 The invention's pyrazolyl compounds are found to show usefulness as p38 kinase inhibitors.

### Description of the Invention

A class of substituted pyrazolyl compounds useful in  
15 treating p38 mediated disorders is defined by Formula IA:



wherein

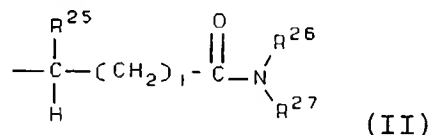
R<sup>1</sup> is selected from hydrido, hydroxy, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heterocyclyl, cycloalkylalkylene, cycloalkenylalkylene, heterocyclylalkylene, haloalkyl, haloalkenyl, haloalkynyl, hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, aralkyl, aralkenyl, aralkynyl, arylheterocyclyl, carboxy, carboxyalkyl, alkoxyalkyl, alkenoxyalkyl, alkynoxyalkyl, aryloxyalkyl, alkoxyaryl, heterocyclyloxyalkyl, alkoxyalkoxy, mercaptoalkyl, alkylthioalkylene, alkenylthioalkylene, alkylthioalkenylene, amino, aminoalkyl, alkylamino,

20

25

alkenylamino, alkynylamino, arylamino, heterocyclylamino,  
 alkylsulfinyl, alkenylsulfinyl, alkynylsulfinyl,  
 arylsulfinyl, heterocyclylsulfinyl, alkylsulfonyl,  
 alkenylsulfonyl, alkynylsulfonyl, arylsulfonyl,  
 5 heterocyclylsulfonyl, alkylaminoalkylene,  
 alkylsulfonylalkylene, acyl, acyloxy carbonyl,  
 alkoxy carbonylalkylene, aryloxy carbonylalkylene,  
 heterocycliloxy carbonylalkylene, alkoxy carbonylarylene,  
 aryloxy carbonylarylene, heterocycliloxy carbonylarylene,  
 10 alkylcarbonylalkylene, arylcarbonylalkylene,  
 heterocyclylcarbonylalkylene, alkylcarbonylarylene,  
 arylcarbonylarylene, heterocyclylcarbonylarylene,  
 alkylcarbonyloxyalkylene, arylcarbonyloxyalkylene,  
 heterocyclylcarbonyloxyalkylene, alkylcarbonyloxyarylene,  
 15 arylcarbonyloxyarylene, and  
 heterocyclylcarbonyloxyarylene; or

R<sup>1</sup> has the formula



wherein:

- 20 i is an integer from 0 to 9;  
 R<sup>25</sup> is selected from hydrogen, alkyl, aralkyl,  
 heterocyclylalkyl, alkoxyalkylene, aryloxyalkylene,  
 aminoalkyl, alkylaminoalkyl, arylaminoalkyl,  
 alkylcarbonylalkylene, arylcarbonylalkylene, and  
 25 heterocyclylcarbonylaminoalkylene; and  
 R<sup>26</sup> is selected from hydrogen, alkyl, alkenyl,  
 alkynyl, cycloalkylalkylene, aralkyl,  
 alkoxy carbonylalkylene, and alkylaminoalkyl; and  
 R<sup>27</sup> is selected from alkyl, cycloalkyl, alkynyl,  
 30 aryl, heterocyclyl, aralkyl, cycloalkylalkylene,  
 cycloalkenylalkylene, cycloalkylarylene,  
 cycloalkylcycloalkyl, heterocyclylalkylene, alkylarylene,  
 alkylaralkyl, aralkylarylene, alkylheterocyclyl,

alkylheterocyclylalkylene, alkylheterocyclylarylene,  
aralkylheterocyclyl, alkoxyalkylene, alkoxyarylene,  
alkoxyaralkyl, alkoxyheterocyclyl, alkoxyalkoxyarylene,  
aryloxyarylene, aralkoxyarylene,  
5 alkoxyheterocyclylalkylene, aryloxyalkoxyarylene,  
alkoxycarbonylalkylene, alkoxycarbonylheterocyclyl,  
alkoxycarbonylheterocyclylcarbonylalkylene, aminoalkyl,  
alkylaminoalkylene, arylaminocarbonylalkylene,  
alkoxyarylaminoalkylene, aminocarbonylalkylene,  
10 arylaminocarbonylalkylene, alkylaminocarbonylalkylene,  
arylcarbonylalkylene, alkoxycarbonylarylene,  
aryloxycarbonylarylene, alkylaryloxycarbonylarylene,  
arylcarbonylarylene, alkylarylcarbonylarylene,  
alkoxycarbonylheterocyclylarylene,  
15 alkoxycarbonylalkoxylarylene,  
heterocyclylcarbonylalkylarylene, alkylthioalkylene,  
cycloalkylthioalkylene, alkylthioarylene,  
aralkylthioarylene, heterocyclylthioarylene,  
arylthioalkylarylene, arylsulfonylaminoalkylene,  
20 alkylsulfonylarylene, alkylaminosulfonylarylene; wherein  
said alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl,  
heterocyclylalkylene, alkylheterocyclylarylene,  
alkoxyarylene, aryloxyarylene, arylaminocarbonylalkylene,  
aryloxycarbonylarylene, arylcarbonylarylene,  
25 alkylthioarylene, heterocyclylthioarylene,  
arylthioalkylarylene, and alkylsulfonylarylene groups  
are optionally substituted with one or more radicals  
independently selected from alkyl, halo, haloalkyl,  
alkoxy, keto, amino, nitro, and cyano; or  
30  $R^{27}$  is  $-CHR^{28}R^{29}$  wherein  $R^{28}$  is alkoxycarbonyl, and  $R^{29}$   
is selected from aralkyl, aralkoxyalkylene,  
heterocyclylalkylene, alkylheterocyclylalkylene,  
alkoxycarbonylalkylene, alkylthioalkylene, and  
aralkylthioalkylene; wherein said aralkyl and  
35 heterocyclyl groups are optionally substituted with one  
or more radicals independently selected from alkyl and

nitro; or

$R^{26}$  and  $R^{27}$  together with the nitrogen atom to which they are attached form a heterocycle, wherein said heterocycle is optionally substituted with one or more radicals independently selected from alkyl, aryl, heterocyclyl, heterocyclylalkylene, alkylheterocyclylalkylene, aryloxyalkylene, alkoxyarylene, alkylaryloxyalkylene, alkylcarbonyl, alkoxycarbonyl, aralkoxycarbonyl, alkylamino and alkoxycarbonylamino; wherein said aryl, heterocyclylalkylene and aryloxyalkylene radicals are optionally substituted with one or more radicals independently selected from halogen, alkyl and alkoxy; and

$R^2$  is selected from hydrido, halogen, mercapto, alkyl, alkenyl, alkynyl, aryl, heterocyclyl, haloalkyl, hydroxyalkyl, aralkyl, alkylheterocyclyl, heterocyclylalkyl, heterocyclylheterocyclyl, heterocyclylalkylheterocyclyl, alkylamino, alkenylamino, alkynylamino, arylamino, aryl(hydroxyalkyl)amino, heterocyclylamino, heterocyclylalkylamino, aralkylamino, N-alkyl-N-alkynyl-amino, aminoalkyl, aminoaryl, aminoalkylamino, aminocarbonylalkylene, arylaminoalkylene, alkylaminoalkylene, arylaminoarylene, alkylaminoarylene, alkylaminoalkylamino, alkylcarbonylaminoalkylene, aminoalkylcarbonylaminoalkylene, alkylaminoalkylcarbonylamino, cycloalkyl, cycloalkenyl, aminoalkylthio, alkylaminocarbonylalkylthio, alkylaminoalkylaminocarbonylalkylthio, alkoxy, heterocyclylloxy, alkylthio, cyanoalkylthio, alkenylthio, alkynylthio, carboxyalkylthio, arylthio, heterocyclylthio, alkoxycarbonylalkylthio, alkylsulfinyl, alkylsulfonyl, carboxy, carboxyalkyl, alkoxyalkyl, alkoxyalkylthio, carboxycycloalkyl, carboxycycloalkenyl, carboxyalkylamino, alkoxycarbonyl, heterocyclylcarbonyl,

alkoxycarbonylalkyl, alkoxycarbonylalkylamino,  
 alkoxycarbonylheterocyclyl,  
 alkoxycarbonylheterocyclylcarbonyl, alkoxyalkylamino,  
 alkoxycarbonylaminoalkylene, alkoxycarbonylaminoalkoxy,  
 5 alkoxycarbonylaminoalkylamino, heterocyclylsulfonyl,  
 aralkythio, heterocyclylalkylthio, aminoalkoxy,  
 cyanoalkoxy, carboxyalkoxy, aryloxy, aralkoxy,  
 alkenyloxy, alkynyloxy, and heterocyclylalkyloxy; wherein  
 the aryl, heterocyclyl, heterocyclylalkyl, cycloalkyl and  
 10 cycloalkenyl groups are optionally substituted with one  
 or more radicals independently selected from halo, keto,  
 amino, alkyl, alkenyl, alkynyl, aryl, heterocyclyl,  
 aralkyl, heterocyclylalkyl, epoxyalkyl,  
 amino(hydroxyalkyl) carboxy, alkoxy, aryloxy, aralkoxy,  
 15 haloalkyl, alkylamino, alkynylamino,  
 alkylaminoalkylamino, heterocyclylalkylamino,  
 alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl,  
 arylsulfonyl, and aralkylsulfonyl; or

$R^2$  is  $R^{200}$ -heterocyclyl- $R^{201}$ ,  $R^{200}$ -aryl- $R^{201}$ , or  $R^{200}$ -  
 20 cycloalkyl- $R^{201}$  wherein:

$R^{200}$  is selected from:

- $(CR^{202}R^{203})_y-$ ;
- $C(O)-$ ;
- $C(O)-(CH_2)_y-$ ;
- 25 -  $C(O)-O-(CH_2)_y-$ ;
- $(CH_2)_y-C(O)-$ ;
- $O-(CH_2)_y-C(O)-$ ;
- $NR^{202}-$ ;
- $NR^{202}-(CH_2)_y-$ ;
- 30 -  $(CH_2)_y-NR^{202}-$ ;
- $(CH_2)_y-NR^{202}-(CH_2)_z-$ ;
- $(CH_2)_y-C(O)-NR^{202}-(CH_2)_z-$ ;
- $(CH_2)_y-NR^{202}-C(O)-(CH_2)_z-$ ;
- $(CH_2)_y-NR^{202}-C(O)-NR^{203}-(CH_2)_z-$ ;
- 35 -  $S(O)_x-(CR^{202}R^{203})_y-$ ;
- $(CR^{202}R^{203})_y-S(O)_x-$ ;

-S(O)<sub>x</sub>-(CR<sup>202</sup>R<sup>203</sup>)<sub>y</sub>-O-;  
 -S(O)<sub>x</sub>-(CR<sup>202</sup>R<sup>203</sup>)<sub>y</sub>-C(O)-;  
 -O-(CH<sub>2</sub>)<sub>y</sub>-;  
 -(CH<sub>2</sub>)<sub>y</sub>-O-;

5 -S-;

-O-;

or R<sup>200</sup> represents a bond;

R<sup>201</sup> represents one or more radicals selected from  
 the group consisting of hydrido, halogen, hydroxy,  
 10 carboxy, keto, alkyl, hydroxyalkyl, haloalkyl,  
 cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl,  
 aralkyl, heterocyclylalkylene, alkylcarbonyl,  
 hydroxyalkylcarbonyl, cycloalkylcarbonyl, arylcarbonyl,  
 haloarylcarbonyl, alkoxy, alkoxyalkylene, alkoxyarylene,  
 15 alkoxy carbonyl, carboxyalkylcarbonyl,  
 alkoxyalkylcarbonyl, heterocyclylalkylcarbonyl,  
 alkylsulfonyl, alkylsulfonylalkylene, amino, aminoalkyl,  
 alkylamino, aralkylamino, alkylaminoalkylene,  
 aminocarbonyl, alkylcarbonylamino,  
 20 alkylcarbonylaminoalkylene, alkylaminoalkylcarbonyl,  
 alkylaminoalkylcarbonylamino,  
 aminoalkylcarbonylaminoalkyl, alkoxy carbonylamino,  
 alkoxyalkylcarbonylamino, alkoxy carbonylaminoalkylene,  
 alkylimidocarbonyl, amidino, alkylamidino,  
 25 aralkylamidino, guanidino, guanidinoalkylene, or  
 alkylsulfonylamino; and

R<sup>202</sup> and R<sup>203</sup> are independently selected from hydrido,  
 alkyl, aryl and aralkyl; and

y and z are independently 0, 1, 2, 3, 4, 5 or 6

30 wherein y + z is less than or equal to 6; and

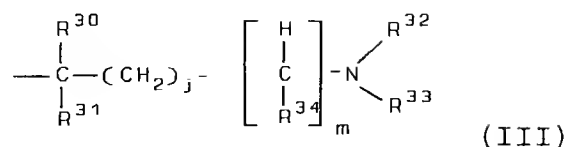
z is 0, 1 or 2; or

R<sup>2</sup> is -NHCR<sup>204</sup>R<sup>205</sup> wherein R<sup>204</sup> is alkylaminoalkylene,  
 and R<sup>205</sup> is aryl; or

R<sup>2</sup> is -C(NR<sup>206</sup>)R<sup>207</sup> wherein R<sup>206</sup> is selected from  
 35 hydrogen and hydroxy, and R<sup>207</sup> is selected from alkyl,  
 aryl and aralkyl; or



R<sup>2</sup> has the formula:



wherein:

j is an integer from 0 to 8; and

5 m is 0 or 1; and

R<sup>30</sup> and R<sup>31</sup> are independently selected from hydrogen, alkyl, aryl, heterocyclyl, aralkyl, heterocyclylalkylene, aminoalkyl, alkylaminoalkyl, aminocarbonylalkyl, alkoxyalkyl, and alkylcarbonyloxyalkyl; and

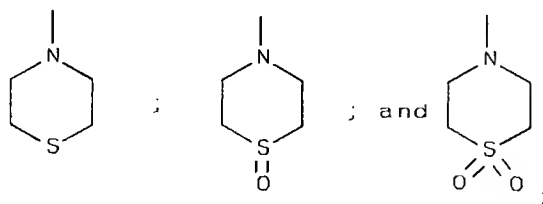
10 R<sup>32</sup> is selected from hydrogen, alkyl, aralkyl, heterocyclylalkyl, alkoxyalkylene, aryloxyalkylene, aminoalkyl, alkylaminoalkyl, arylaminoalkyl, alkylcarbonylalkylene, arylcarbonylalkylene, and heterocyclylcarbonylaminoalkylene;

15 R<sup>33</sup> is selected from hydrogen, alkyl, -C(O)R<sup>35</sup>, -C(O)OR<sup>35</sup>, -SO<sub>2</sub>R<sup>36</sup>, -C(O)NR<sup>37</sup>R<sup>38</sup>, and -SO<sub>2</sub>NR<sup>39</sup>R<sup>40</sup>, wherein R<sup>35</sup>, R<sup>36</sup>, R<sup>37</sup>, R<sup>38</sup>, R<sup>39</sup> and R<sup>40</sup> are independently selected from hydrocarbon, heterosubstituted hydrocarbon and heterocyclyl; and

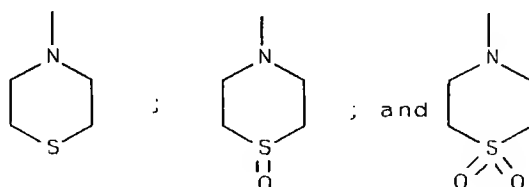
20 R<sup>34</sup> is selected from hydrogen, alkyl, aminocarbonyl, alkylaminocarbonyl, and arylaminocarbonyl; or

R<sup>2</sup> is -CR<sup>41</sup>R<sup>42</sup> wherein R<sup>41</sup> is aryl, and R<sup>42</sup> is hydroxy; and

25 R<sup>3</sup> is selected from pyridinyl, pyrimidinyl, quinolinyl, purinyl, maleimidyl, pyridonyl, thiazolyl, thiazolylalkyl, thiazolylamino,



wherein the R<sup>3</sup> pyridinyl, pyrimidinyl, quinolinyl, purinyl, maleimidyl, pyridonyl, thiazolyl, thiazolylalkyl, thiazolylamino,



5 groups are optionally substituted with one or more radicals independently selected from halo, keto, alkyl, aralkyl, aralkenyl, arylheterocyclyl, carboxy, carboxyalkyl, alkoxy, aryloxy, alkylthio, arylthio, alkylsulfinyl, arylsulfinyl, alkylsulfonyl, arylsulfonyl, 10 aralkoxy, heterocyclylalkoxy, amino, alkylamino, alkenylamino, alkynylamino, cycloalkylamino, cycloalkenylamino, arylamino, haloaryl amino, heterocyclylamino, aminocarbonyl, cyano, hydroxy, hydroxyalkyl, alkoxyalkylene, alkenoxyalkylene, 15 aryloxyalkyl, alkoxyalkylamino, alkylaminoalkoxy, alkoxycarbonyl, aryloxycarbonyl, heterocyclylloxycarbonyl, alkoxycarbonylamino, alkoxyarylamino, alkoxyaralkylamino, aminosulfinyl, aminosulfonyl, alkylsulfonylamino, alkylaminoalkylamino, hydroxyalkylamino, aralkylamino, 20 aryl(hydroxyalkyl)amino, alkylaminoalkylaminoalkylamino, alkylheterocyclylamino, heterocyclylalkylamino, alkylheterocyclylalkylamino, aralkylheterocyclylamino, heterocyclylheterocyclylalkylamino, alkoxycarbonylheterocyclylamino, nitro, 25 alkylaminocarbonyl, alkylcarbonylamino, haloalkylsulfonyl, aminoalkyl, haloalkyl, alkylcarbonyl, hydrazinyl, alkylhydrazinyl, arylhydrazinyl, or -NR<sup>44</sup>R<sup>45</sup> wherein R<sup>44</sup> is alkylcarbonyl or amino, and R<sup>45</sup> is alkyl or aralkyl; and

30 R<sup>4</sup> is selected from hydrido, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, and heterocyclyl, wherein

R<sup>4</sup> is optionally substituted with one or more radicals independently selected from halo, alkyl, alkenyl, alkynyl, aryl, heterocyclyl, alkylthio, arylthio, alkylthioalkylene, arylthioalkylene, alkylsulfinyl, alkylsulfinylalkylene, arylsulfinylalkylene, alkylsulfonyl, alkylsulfonylalkylene, arylsulfonylalkylene, alkoxy, aryloxy, aralkoxy, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkoxycarbonyl, aryloxycarbonyl, haloalkyl, amino, cyano, nitro, alkylamino, arylamino, alkylaminoalkylene, arylaminoalkylene, aminoalkylamino, and hydroxy;

provided R<sup>3</sup> is not 2-pyridinyl when R<sup>4</sup> is a phenyl ring containing a 2-hydroxy substituent and when R<sup>1</sup> is hydrido; and

further provided R<sup>2</sup> is selected from aryl, heterocyclyl, unsubstituted cycloalkyl and cycloalkenyl when R<sup>4</sup> is hydrido; and

further provided that R<sup>4</sup> is not methylsulfonylphenyl or aminosulfonylphenyl; and

further provided that R<sup>1</sup> is not methylsulfonylphenyl; or

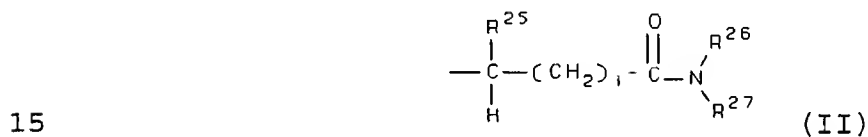
a pharmaceutically-acceptable salt or tautomer thereof.

In a subclass of interest, R<sup>2</sup> is as defined above, and

R<sup>1</sup> is selected from hydrido, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkylalkylene, cycloalkenylalkylene, heterocyclylalkylene, haloalkyl, haloalkenyl, haloalkynyl, hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, aralkyl, aralkenyl, aralkynyl, arylheterocyclyl, carboxy, carboxyalkyl, alkoxyalkyl, alkenoxyalkyl, alkynoxyalkyl, aryloxyalkyl, heterocycliloxyalkyl, alkoxyalkoxy, mercaptoalkyl, alkylthioalkylene, alkenylthioalkylene, alkylthioalkenylene, amino, aminoalkyl, alkylamino,

alkenylamino, alkynylamino, arylamino, heterocyclylamino,  
 alkylsulfinyl, alkenylsulfinyl, alkynylsulfinyl,  
 arylsulfinyl, heterocyclylsulfinyl, alkylsulfonyl,  
 alkenylsulfonyl, alkynylsulfonyl, arylsulfonyl,  
 5 heterocyclylsulfonyl, alkylaminoalkylene,  
 alkylsulfonylalkylene, acyl, acyloxycarbonyl,  
 alkoxycarbonylalkylene, aryloxycarbonylalkylene,  
 heterocyclylloxycarbonylalkylene, alkylcarbonylalkylene,  
 arylcarbonylalkylene, heterocyclylcarbonylalkylene,  
 10 alkylcarbonyloxyalkylene, arylcarbonyloxyalkylene,  
 heterocyclylcarbonyloxyalkylene, alkylcarbonyloxyarylene,  
 arylcarbonyloxyarylene, and  
 heterocyclylcarbonyloxyarylene; or

R<sup>1</sup> has the formula



wherein:

i is an integer from 0 to 9;

R<sup>25</sup> is selected from hydrogen, alkyl, aralkyl,  
 heterocyclylalkyl, alkoxyalkylene, aryloxyalkylene,  
 20 aminoalkyl, alkylaminoalkyl, arylaminoalkyl,  
 alkylcarbonylalkylene, arylcarbonylalkylene, and  
 heterocyclylcarbonylaminoalkylene; and

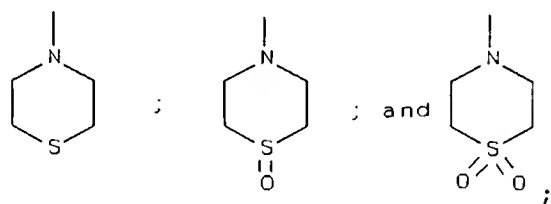
R<sup>26</sup> is selected from hydrogen, alkyl, alkenyl,  
 alkynyl, cycloalkylalkylene, aralkyl,  
 25 alkoxycarbonylalkylene, and alkylaminoalkyl; and

R<sup>27</sup> is selected from alkyl, cycloalkyl, alkynyl,  
 aryl, heterocyclyl, aralkyl, cycloalkylalkylene,  
 cycloalkenylalkylene, cycloalkylarylene,  
 cycloalkylcycloalkyl, heterocyclylalkylene, alkylarylene,  
 30 alkylaralkyl, aralkylarylene, alkylheterocyclyl,  
 alkylheterocyclylalkylene, alkylheterocyclylarylene,  
 aralkylheterocyclyl, alkoxyalkylene, alkoxyarylene,  
 alkoxyaralkyl, alkoxyheterocyclyl, alkoxyalkoxyarylene,

aryloxyarylene, aralkoxyarylene,  
 alkoxyheterocyclylalkylene, aryloxyalkoxyarylene,  
 alkoxycarbonylalkylene, alkoxycarbonylheterocyclyl,  
 alkoxycarbonylheterocyclylcarbonylalkylene, aminoalkyl,  
 5 alkylaminoalkylene, arylaminocarbonylalkylene,  
 alkoxyarylaminoalkylene, aminocarbonylalkylene,  
 arylaminocarbonylalkylene, alkylaminocarbonylalkylene,  
 arylcarbonylalkylene, alkoxycarbonylarylene,  
 aryloxycarbonylarylene, alkylaryloxycarbonylarylene,  
 10 arylcarbonylarylene, alkylarylcarbonylarylene,  
 alkoxycarbonylheterocyclylarylene,  
 alkoxycarbonylalkoxylarylene,  
 heterocyclylcarbonylalkylarylene, alkylthioalkylene,  
 cycloalkylthioalkylene, alkylthioarylene,  
 15 aralkylthioarylene, heterocyclylthioarylene,  
 arylthioalkylarylene, arylsulfonylaminoalkylene,  
 alkylsulfonylarylene, alkylaminosulfonylarylene; wherein  
 said alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl,  
 heterocyclylalkylene, alkylheterocyclylarylene,  
 20 alkoxyarylene, aryloxyarylene, arylaminocarbonylalkylene,  
 aryloxycarbonylarylene, arylcarbonylarylene,  
 alkylthioarylene, heterocyclylthioarylene,  
 arylthioalkylarylene, and alkylsulfonylarylene groups  
 are optionally substituted with one or more radicals  
 25 independently selected from alkyl, halo, haloalkyl,  
 alkoxy, keto, amino, nitro, and cyano; or  
 $R^{27}$  is  $-CHR^{28}R^{29}$  wherein  $R^{28}$  is alkoxycarbonyl, and  $R^{29}$   
 is selected from aralkyl, aralkoxyalkylene,  
 heterocyclylalkylene, alkylheterocyclylalkylene,  
 30 alkoxycarbonylalkylene, alkylthioalkylene, and  
 aralkylthioalkylene; wherein said aralkyl and  
 heterocyclyl groups are optionally substituted with one  
 or more radicals independently selected from alkyl and  
 nitro; or  
 35  $R^{26}$  and  $R^{27}$  together with the nitrogen atom to which  
 they are attached form a heterocycle, wherein said

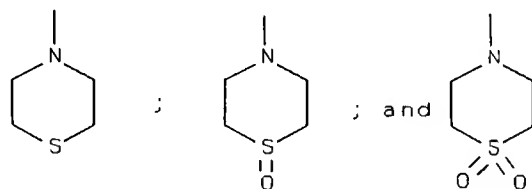
heterocycle is optionally substituted with one or more radicals independently selected from alkyl, aryl, heterocyclyl, heterocyclylalkylene, alkylheterocyclylalkylene, aryloxyalkylene, alkoxyarylene, alkylaryloxyalkylene, alkylcarbonyl, alkoxycarbonyl, aralkoxycarbonyl, alkylamino and alkoxycarbonylamino; wherein said aryl, heterocyclylalkylene and aryloxyalkylene radicals are optionally substituted with one or more radicals independently selected from halogen, alkyl and alkoxy; and

R<sup>3</sup> is selected from pyridinyl, pyrimidinyl, quinolinyl, purinyl, maleimidyl, pyridonyl, thiazolyl, thiazolylalkyl, thiazolylamino,



15

wherein the R<sup>3</sup> pyridinyl, pyrimidinyl, quinolinyl, purinyl, maleimidyl, pyridonyl, thiazolyl, thiazolylalkyl, thiazolylamino,



groups are optionally substituted with one or more radicals independently selected from halo, keto, alkyl, aralkyl, aralkenyl, arylheterocyclyl, carboxy, carboxyalkyl, alkoxy, aryloxy, alkylthio, arylthio, alkylsulfinyl, arylsulfinyl, arylsulfonyl, aralkoxy, heterocyclylalkoxy, amino, alkylamino, alkenylamino,

25

alkynylamino, cycloalkylamino, cycloalkenylamino,  
arylamino, haloarylamino, heterocyclylamino,  
aminocarbonyl, cyano, hydroxy, hydroxyalkyl,  
alkoxyalkylene, alkenoxyalkylene, aryloxyalkyl,  
5 alkoxyalkylamino, alkylaminoalkoxy, alkoxycarbonyl,  
aryloxycarbonyl, heterocyclylloxycarbonyl,  
alkoxycarbonylamino, alkoxyarylamino, alkoxyaralkylamino,  
aminosulfinyl, alkylsulfonylamino, alkylaminoalkylamino,  
hydroxyalkylamino, aralkylamino, aryl(hydroxyalkyl)amino,  
10 alkylaminoalkylaminoalkylamino, alkylheterocyclylamino,  
heterocyclylalkylamino, alkylheterocyclylalkylamino,  
aralkylheterocyclylamino,  
heterocyclylheterocyclylalkylamino,  
alkoxycarbonylheterocyclylamino, nitro,  
15 alkylaminocarbonyl, alkylcarbonylamino, aminoalkyl,  
haloalkyl, alkylcarbonyl, hydrazinyl, alkylhydrazinyl,  
arylhydrazinyl, or  $-NR^{44}R^{45}$  wherein  $R^{44}$  is alkylcarbonyl or  
amino, and  $R^{45}$  is alkyl or aralkyl; and

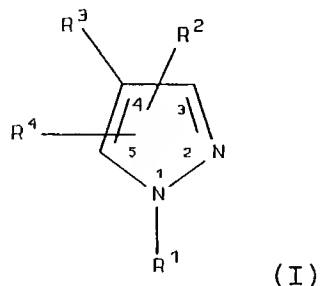
$R^4$  is selected from hydrido, alkyl, alkenyl, alkynyl,  
20 cycloalkyl, cycloalkenyl, aryl, and heterocyclyl, wherein  
 $R^4$  is optionally substituted with one or more radicals  
independently selected from halo, alkyl, alkenyl,  
alkynyl, aryl, heterocyclyl, alkylthio, arylthio,  
alkylthioalkylene, arylthioalkylene, alkylsulfinyl,  
25 alkylsulfinylalkylene, arylsulfinylalkylene,  
alkylsulfonylalkylene, arylsulfonylalkylene, alkoxy,  
aryloxy, aralkoxy, aminocarbonyl, alkylaminocarbonyl,  
arylaminocarbonyl, alkoxycarbonyl, aryloxycarbonyl,  
haloalkyl, amino, cyano, nitro, alkylamino, arylamino,  
30 alkylaminoalkylene, arylaminoalkylene, aminoalkylamino,  
and hydroxy; or

a pharmaceutically-acceptable salt or tautomer  
thereof.

35 In the various embodiments of the present invention,  
the novel compounds generically disclosed herein

preferably do not include those substituted pyrazoles disclosed in WO98/52940 published on November 26, 1998.

A subclass of compounds useful in treating p38 mediated disorders is defined by Formula I:



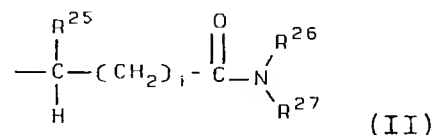
wherein

R¹ is selected from hydrido, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heterocyclyl, cycloalkylalkylene, cycloalkenylalkylene, heterocyclylalkylene, haloalkyl, haloalkenyl, haloalkynyl, hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, aralkyl, aralkenyl, aralkynyl, arylheterocyclyl, carboxy, carboxyalkyl, alkoxyalkyl, alkenoxyalkyl, alkynoxyalkyl, aryloxyalkyl, heterocycliloxyalkyl, alkoxyalkoxy, mercaptoalkyl, alkylthioalkylene, alkenylthioalkylene, alkylthioalkenylene, amino, aminoalkyl, alkylamino, alkenylamino, alkynylamino, arylamino, heterocyclylamino, alkylsulfinyl, alkenylsulfinyl, alkynylsulfinyl, arylsulfinyl, heterocyclylsulfinyl, alkylsulfonyl, alkenylsulfonyl, alkynylsulfonyl, arylsulfonyl, heterocyclylsulfonyl, alkylaminoalkylene, alkylsulfonylalkylene, acyl, acyloxycarbonyl, alkoxycarbonylalkylene, aryloxycarbonylalkylene, heterocycliloxy carbonylalkylene, alkoxycarbonylarylene, aryloxycarbonylarylene, heterocycliloxy carbonylarylene, alkylcarbonylalkylene, arylcarbonylalkylene,



heterocyclylcarbonylalkylene, alkylcarbonylarylene,  
 arylcarbonylarylene, heterocyclylcarbonylarylene,  
 alkylcarbonyloxyalkylene, arylcarbonyloxyalkylene,  
 heterocyclylcarbonyloxyalkylene, alkylcarbonyloxyarylene,  
 5 arylcarbonyloxyarylene, and  
 heterocyclylcarbonyloxyarylene; or

R<sup>1</sup> has the formula



wherein:

10 i is an integer from 0 to 9;

R<sup>25</sup> is selected from hydrogen, alkyl, aralkyl,  
 heterocyclylalkyl, alkoxyalkylene, aryloxyalkylene,  
 aminoalkyl, alkylaminoalkyl, arylaminoalkyl,  
 alkylcarbonylalkylene, arylcarbonylalkylene, and  
 15 heterocyclylcarbonylaminoalkylene; and

R<sup>26</sup> is selected from hydrogen, alkyl, alkenyl,  
 alkynyl, cycloalkylalkylene, aralkyl,  
 alkoxy carbonylalkylene, and alkylaminoalkyl; and

R<sup>27</sup> is selected from alkyl, cycloalkyl, alkynyl,  
 20 aryl, heterocyclyl, aralkyl, cycloalkylalkylene,  
 cycloalkenylalkylene, cycloalkylarylene,  
 cycloalkylcycloalkyl, heterocyclylalkylene, alkylarylene,  
 alkylaralkyl, aralkylarylene, alkylheterocyclyl,  
 alkylheterocyclylalkylene, alkylheterocyclylarylene,  
 25 aralkylheterocyclyl, alkoxyalkylene, alkoxyarylene,  
 alkoxyaralkyl, alkoxyheterocyclyl, alkoxyalkoxyarylene,  
 aryloxyarylene, aralkoxyarylene,  
 alkoxyheterocyclylalkylene, aryloxyalkoxyarylene,  
 alkoxy carbonylalkylene, alkoxy carbonyl heterocyclyl,  
 30 alkoxy carbonyl heterocyclyl carbonylalkylene, aminoalkyl,  
 alkylaminoalkylene, arylaminocarbonylalkylene,  
 alkoxyarylaminocarbonylalkylene, aminocarbonylalkylene,  
 arylaminocarbonylalkylene, alkylaminocarbonylalkylene,

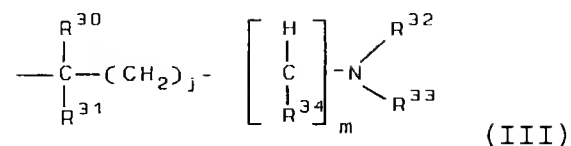
arylcarbonylalkylene, alkoxycarbonylarylene,  
aryloxycarbonylarylene, alkylaryloxycarbonylarylene,  
arylcarbonylarylene, alkylarylcarbonylarylene,  
alkoxycarbonylheterocyclylarylene,  
5 alkoxycarbonylalkoxylarylene,  
heterocyclylcarbonylalkylarylene, alkylthioalkylene,  
cycloalkylthioalkylene, alkylthioarylene,  
aralkylthioarylene, heterocyclylthioarylene,  
arylthioalkylarylene, arylsulfonylaminoalkylene,  
10 alkylsulfonylarylene, alkylaminosulfonylarylene; wherein  
said alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl,  
heterocyclylalkylene, alkylheterocyclylarylene,  
alkoxyarylene, aryloxyarylene, arylaminocarbonylalkylene,  
aryloxycarbonylarylene, arylcarbonylarylene,  
15 alkylthioarylene, heterocyclylthioarylene,  
arylthioalkylarylene, and alkylsulfonylarylene groups  
are optionally substituted with one or more radicals  
independently selected from alkyl, halo, haloalkyl,  
alkoxy, keto, amino, nitro, and cyano; or  
20  $R^{27}$  is  $-CHR^{28}R^{29}$  wherein  $R^{28}$  is alkoxycarbonyl, and  $R^{29}$   
is selected from aralkyl, aralkoxyalkylene,  
heterocyclylalkylene, alkylheterocyclylalkylene,  
alkoxycarbonylalkylene, alkylthioalkylene, and  
aralkylthioalkylene; wherein said aralkyl and  
25 heterocyclyl groups are optionally substituted with one  
or more radicals independently selected from alkyl and  
nitro; or

$R^{26}$  and  $R^{27}$  together with the nitrogen atom to which  
they are attached form a heterocycle, wherein said  
30 heterocycle is optionally substituted with one or more  
radicals independently selected from alkyl, aryl,  
heterocyclyl, heterocyclylalkylene,  
alkylheterocyclylalkylene, aryloxyalkylene,  
alkoxyarylene, alkylaryloxyalkylene, alkylcarbonyl,  
alkoxycarbonyl, aralkoxycarbonyl, alkylamino and  
35 alkoxycarbonylamino; wherein said aryl,

heterocyclylalkylene and aryloxyalkylene radicals are optionally substituted with one or more radicals independently selected from halogen, alkyl and alkoxy; and

- 5           R<sup>2</sup> is selected from hydrido, halogen, alkyl, alkenyl, alkynyl, aryl, heterocyclyl, haloalkyl, hydroxyalkyl, aralkyl, alkylheterocyclyl, heterocyclylalkyl, alkylamino, alkenylamino, alkynylamino, arylamino, heterocyclylamino, heterocyclylalkylamino, aralkylamino, 10 aminoalkyl, aminoaryl, aminoalkylamino, arylaminoalkylene, alkylaminoalkylene, arylaminoarylene, alkylaminoarylene, alkylaminoalkylamino, cycloalkyl, cycloalkenyl, alkoxy, heterocycliloxy, alkylthio, arylthio, heterocyclylthio, carboxy, carboxyalkyl, 15 carboxycycloalkyl, carboxycycloalkenyl, carboxyalkylamino, alkoxycarbonyl, heterocyclylcarbonyl, alkoxycarbonylalkyl, alkoxycarbonylheterocyclyl, alkoxycarbonylheterocyclylcarbonyl, alkoxylalkylamino, alkoxycarbonylaminoalkylamino, and heterocyclylsulfonyl; 20 wherein the aryl, heterocyclyl, heterocyclylalkyl, cycloalkyl and cycloalkenyl groups are optionally substituted with one or more radicals independently selected from halo, keto, amino, alkyl, alkenyl, alkynyl, aryl, heterocyclyl, aralkyl, heterocyclylalkyl, 25 epoxyalkyl, amino(hydroxyalkyl) carboxy, alkoxy, aryloxy, aralkoxy, haloalkyl, alkylamino, alkynylamino, alkylaminoalkylamino, heterocyclylalkylamino, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, and aralkylsulfonyl; or

R<sup>2</sup> has the formula:



wherein:

j is an integer from 0 to 8; and

5 m is 0 or 1; and

R<sup>30</sup> and R<sup>31</sup> are independently selected from hydrogen, alkyl, aryl, heterocyclyl, aralkyl, heterocyclylalkylene, aminoalkyl, alkylaminoalkyl, aminocarbonylalkyl, alkoxyalkyl, and alkylcarbonyloxyalkyl; and

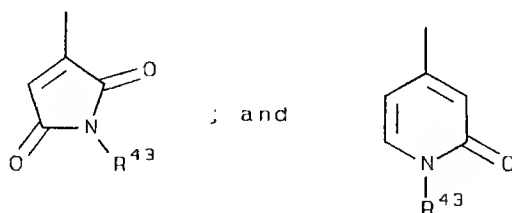
10 R<sup>32</sup> is selected from hydrogen, alkyl, aralkyl, heterocyclylalkyl, alkoxyalkylene, aryloxyalkylene, aminoalkyl, alkylaminoalkyl, arylaminoalkyl, alkylcarbonylalkylene, arylcarbonylalkylene, and heterocyclylcarbonylaminoalkylene;

15 R<sup>33</sup> is selected from hydrogen, alkyl, -C(O)R<sup>35</sup>, -C(O)OR<sup>35</sup>, -SO<sub>2</sub>R<sup>36</sup>, -C(O)NR<sup>37</sup>R<sup>38</sup>, and -SO<sub>2</sub>NR<sup>39</sup>R<sup>40</sup>, wherein R<sup>35</sup>, R<sup>36</sup>, R<sup>37</sup>, R<sup>38</sup>, R<sup>39</sup> and R<sup>40</sup> are independently selected from hydrocarbon, heterosubstituted hydrocarbon and heterocyclyl; and

20 R<sup>34</sup> is selected from hydrogen, alkyl, aminocarbonyl, alkylaminocarbonyl, and arylaminocarbonyl; or

R<sup>2</sup> is -CR<sup>41</sup>R<sup>42</sup> wherein R<sup>41</sup> is aryl, and R<sup>42</sup> is hydroxy; and

25 R<sup>3</sup> is selected from pyridinyl, pyrimidinyl, quinolinyl, purinyl,



(IV)

(V)

wherein  $R^{43}$  is selected from hydrogen, alkyl, aminoalkyl, alkoxyalkyl, alkenoxyalkyl, and aryloxyalkyl; and

5        wherein the  $R^3$  pyridinyl, pyrimidinyl, quinolinyl and purinyl groups are optionally substituted with one or more radicals independently selected from halo, alkyl, aralkyl, aralkenyl, arylheterocyclyl, carboxy, carboxyalkyl, alkoxy, aryloxy, alkylthio, arylthio, 10 alkylsulfinyl, arylsulfinyl, alkylsulfonyl, arylsulfonyl, aralkoxy, heterocyclylalkoxy, amino, alkylamino, alkenylamino, alkynylamino, cycloalkylamino, cycloalkenylamino, arylamino, heterocyclylamino, aminocarbonyl, cyano, hydroxy, hydroxyalkyl, 15 alkoxycarbonyl, aryloxycarbonyl, heterocyclylloxycarbonyl, alkoxycarbonylamino, alkoxyaralkylamino, aminosulfinyl, aminosulfonyl, alkylaminoalkylamino, hydroxyalkylamino, aralkylamino, heterocyclylalkylamino, aralkylheterocyclylamino, nitro, alkylaminocarbonyl, 20 alkylcarbonylamino, halosulfonyl, aminoalkyl, haloalkyl, alkylcarbonyl, hydrazinyl, alkylhydrazinyl, arylhydrazinyl, or  $-NR^{44}R^{45}$  wherein  $R^{44}$  is alkylcarbonyl or amino, and  $R^{45}$  is alkyl or aralkyl; and

$R^4$  is selected from hydrido, alkyl, alkenyl, alkynyl, 25 cycloalkyl, cycloalkenyl, aryl, and heterocyclyl, wherein  $R^4$  is optionally substituted with one or more radicals independently selected from halo, alkyl, alkenyl, alkynyl, aryl, heterocyclyl, alkylthio, arylthio, alkylthioalkylene, arylthioalkylene, alkylsulfinyl, 30 alkylsulfinylalkylene, arylsulfinylalkylene, alkylsulfonyl, alkylsulfonylalkylene, arylsulfonylalkylene, alkoxy, aryloxy, aralkoxy, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkoxycarbonyl, aryloxycarbonyl, haloalkyl, amino, cyano, 35 nitro, alkylamino, arylamino, alkylaminoalkylene, arylaminoalkylene, aminoalkylamino, and hydroxy;

provided R<sup>3</sup> is not 2-pyridinyl when R<sup>4</sup> is a phenyl ring containing a 2-hydroxy substituent and when R<sup>1</sup> is hydrido; further provided R<sup>2</sup> is selected from aryl, heterocyclyl, unsubstituted cycloalkyl and cycloalkenyl  
5 when R<sup>4</sup> is hydrido; and further provided R<sup>4</sup> is not methylsulfonylphenyl; or

a pharmaceutically-acceptable salt or tautomer thereof.

10 Compounds of Formula I and/or IA would be useful for, but not limited to, the treatment of any disorder or disease state in a human, or other mammal, which is excacerbated or caused by excessive or unregulated TNF or p38 kinase production by such mammal. Accordingly, the  
15 present invention provides a method of treating a cytokine-mediated disease which comprises administering an effective cytokine-interfering amount of a compound of Formula I and/or 1A or a pharmaceutically acceptable salt thereof.

20 Compounds of Formula I and/or IA would be useful for, but not limited to, the treatment of inflammation in a subject, as an analgesic in the treatment of pain including but not limited to neuropathic pain, and for use as antipyretics for the treatment of fever.

25 Compounds of the invention would be useful to treat arthritis, including but not limited to, rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis, osteoarthritis, gouty arthritis and other  
30 arthritic conditions. Such compounds would be useful for the treatment of pulmonary disorders or lung inflammation, including adult respiratory distress syndrome, pulmonary sarcoisosis, asthma, silicosis, and chronic pulmonary inflammatory disease. The compounds  
35 are also useful for the treatment of viral and bacterial infections, including sepsis, septic shock, gram negative

sepsis, malaria, meningitis, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), pneumonia, and herpesvirus. The  
5 compounds are also useful for the treatment of bone resorption diseases, such as osteoporosis, endotoxic shock, toxic shock syndrome, reperfusion injury, autoimmune disease including graft vs. host reaction and allograft rejections, cardiovascular diseases including  
10 atherosclerosis, myocardial infarction, thrombosis, congestive heart failure, and cardiac reperfusion injury, renal reperfusion injury, liver disease and nephritis, and myalgias due to infection.

The compounds are also useful for the treatment of  
15 influenza, multiple sclerosis, leukemia, lymphoma, diabetes, systemic lupus erythematosus (SLE), neuroinflammation, ischemia including stroke and brain ischemia, brain trauma, brain edema, skin-related conditions such as psoriasis, eczema, burns, dermatitis,  
20 keloid formation, scar tissue formation, and angiogenic disorders. Compounds of the invention also would be useful to treat gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis. The  
25 compounds would also be useful in the treatment of ophthalmic diseases, such as retinitis, retinopathies, uveitis, ocular photophobia, and of acute injury to the eye tissue. Compounds of the invention also would be useful for treatment of angiogenesis, including  
30 neoplasia; metastasis; ophthalmological conditions such as corneal graft rejection, ocular neovascularization, retinal neovascularization including neovascularization following injury or infection, diabetic retinopathy, retrolental fibroplasia and neovascular glaucoma;  
35 ulcerative diseases such as gastric ulcer; pathological, but non-malignant, conditions such as hemangiomas,

including invantile hemaginomas, angiofibroma of the nasopharynx and avascular necrosis of bone; diabetic nephropathy and cardiomyopathy; and disorders of the female reproductive system such as endometriosis. The compounds of the invention may also be useful for preventing the production of cyclooxygenase-2.

Compounds of the invention would be useful for the prevention or treatment of benign and malignant tumors/neoplasia including cancer, such as colorectal cancer, brain cancer, bone cancer, epithelial cell-derived neoplasia (epithelial carcinoma) such as basal cell carcinoma, adenocarcinoma, gastrointestinal cancer such as lip cancer, mouth cancer, esophageal cancer, small bowel cancer and stomach cancer, colon cancer, liver cancer, bladder cancer, pancreas cancer, ovarian cancer, cervical cancer, lung cancer, breast cancer and skin cancer, such as squamus cell and basal cell cancers, prostate cancer, renal cell carcimoma, and other known cancers that affect epithelial cells throughout the body.

The compounds of the invention also would be useful for the treatment of certain central nervous system disorders such as Alzheimer's disease and Parkinson's disease.

Besides being useful for human treatment, these compounds are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. More preferred animals include horses, dogs, and cats.

The present compounds may also be used in co-therapies, partially or completely, in place of other conventional anti-inflammatories, such as together with steroids, cyclooxygenase-2 inhibitors, DMARD's, immunosuppressive agents, NSAIDs, 5-lipoxygenase inhibitors, LTB<sub>4</sub> antagonists and LTA<sub>4</sub> hydrolase inhibitors.

As used herein, the term "TNF mediated disorder"



refers to any and all disorders and disease states in which TNF plays a role, either by control of TNF itself, or by TNF causing another monokine to be released, such as but not limited to IL-1, IL-6 or IL-8. A disease state in which, for instance, IL-1 is a major component, and whose production or action, is exacerbated or secreted in response to TNF, would therefore be considered a disorder mediated by TNF.

As used herein, the term "p38 mediated disorder" refers to any and all disorders and disease states in which p38 plays a role, either by control of p38 itself, or by p38 causing another factor to be released, such as but not limited to IL-1, IL-6 or IL-8. A disease state in which, for instance, IL-1 is a major component, and whose production or action, is exacerbated or secreted in response to p38, would therefore be considered a disorder mediated by p38.

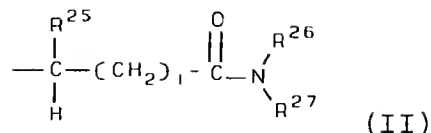
As TNF- $\beta$  has close structural homology with TNF- $\alpha$  (also known as cachectin) and since each induces similar biologic responses and binds to the same cellular receptor, the synthesis of both TNF- $\alpha$  and TNF- $\beta$  are inhibited by the compounds of the present invention and thus are herein referred to collectively as "TNF" unless specifically delineated otherwise.

A preferred class of compounds consists of those compounds of Formula I wherein

R<sup>1</sup> is selected from hydrido, lower alkyl, lower cycloalkyl, lower alkenyl, lower alkynyl, lower heterocyclyl, lower cycloalkylalkylene, lower haloalkyl, lower hydroxyalkyl, lower aralkyl, lower alkoxyalkyl, lower mercaptoalkyl, lower alkylthioalkylene, amino, lower alkylamino, lower arylamino, lower alkylaminoalkylene, and lower heterocyclylalkylene; or

R<sup>1</sup> has the formula

27



wherein:

i is 0, 1 or 2; and

R<sup>25</sup> is selected from hydrogen, lower alkyl, lower  
 5 phenylalkyl, lower heterocyclalkyl, lower  
 alkoxyalkylene, lower phenoxyalkylene, lower aminoalkyl,  
 lower alkylaminoalkyl, lower phenoxyaminoalkyl, lower  
 alkylcarbonylalkylene, lower phenoxycarbonylalkylene, and  
 lower heterocyclalkylcarbonylaminoalkylene; and

10 R<sup>26</sup> is selected from hydrogen, lower alkyl, lower  
 alkenyl, lower alkynyl, lower cycloalkylalkylene, lower  
 phenylalkyl, lower alkoxycarbonylalkylene, and lower  
 alkylaminoalkyl; and

R<sup>27</sup> is selected from lower alkyl, lower cycloalkyl,  
 15 lower alkynyl, aryl selected from phenyl, biphenyl and  
 naphthyl, lower heterocycl, lower phenylalkyl, lower  
 cycloalkylalkylene, lower cycloalkenylalkylene, lower  
 cycloalkylarylene, lower cycloalkylcycloalkyl, lower  
 heterocyclalkylene, lower alkylphenylene, lower  
 20 alkylphenylalkyl, lower phenylalkylphenylene, lower  
 alkylheterocycl, lower alkylheterocyclalkylene, lower  
 alkylheterocyclphenylene, lower  
 phenylalkylheterocycl, lower alkoxyalkylene, lower  
 alkoxyphenylene, lower alkoxyphenylalkyl, lower  
 25 alkoxyheterocycl, lower alkoxyalkoxyphenylene, lower  
 phenoxyphenylene, lower phenylalkoxyphenylene, lower  
 alkoxyheterocyclalkylene, lower phenoxyalkoxyphenylene,  
 lower alkoxycarbonylalkylene, lower  
 alkoxycarbonylheterocycl, lower  
 30 alkoxycarbonylheterocyclcarbonylalkylene, lower  
 aminoalkyl, lower alkylaminoalkylene, lower  
 phenylaminocarbonylalkylene, lower  
 alkoxyphenylaminocarbonylalkylene, lower

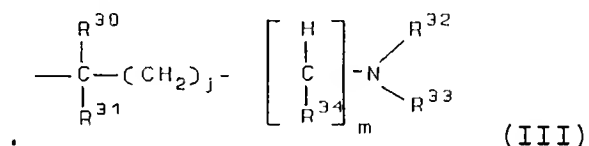
- aminocarbonylalkylene, arylaminocarbonylalkylene, lower  
alkylaminocarbonylalkylene, lower phenylcarbonylalkylene,  
lower alkoxycarbonylphenylene, lower  
phenoxycarbonylphenylene, lower  
5 alkylphenoxycarbonylphenylene, lower  
phenylcarbonylphenylene, lower  
alkylphenylcarbonylphenylene, lower  
alkoxycarbonylheterocyclylphenylene, lower  
alkoxycarbonylalkoxylphenylene, lower  
10 heterocyclylcarbonylalkylphenylene, lower  
alkylthioalkylene, cycloalkylthioalkylene, lower  
alkylthiophenylene, lower phenylalkylthiophenylene, lower  
heterocyclylthiophenylene, lower  
phenylthioalkylphenylene, lower  
15 phenylsulfonylaminoalkylene, lower  
alkylsulfonylphenylene, lower  
alkylaminosulfonylphenylene; wherein said lower alkyl,  
lower cycloalkyl, aryl selected from phenyl, biphenyl and  
naphthyl, lower heterocyclyl, lower phenylalkyl, lower  
20 heterocyclylalkylene, lower alkylheterocyclylphenylene,  
lower alkoxyphenylene, lower phenoxyphenylene, lower  
phenylaminocarbonylalkylene, lower  
phenoxycarbonylphenylene, lower phenylcarbonylphenylene,  
lower alkylthiophenylene, lower  
25 heterocyclylthiophenylene, lower  
phenylthioalkylphenylene, and lower  
alkylsulfonylphenylene groups are optionally substituted  
with one or more radicals independently selected from  
lower alkyl, halo, lower haloalkyl, lower alkoxy, keto,  
30 amino, nitro, and cyano; or  
R<sup>27</sup> is -CHR<sup>46</sup>R<sup>47</sup> wherein R<sup>46</sup> is lower alkoxycarbonyl,  
and R<sup>47</sup> is selected from lower phenylalkyl, lower  
phenylalkoxyalkylene, lower heterocyclylalkylene, lower  
alkylheterocyclylalkylene, lower alkoxycarbonylalkylene,  
35 lower alkylthioalkylene, and lower  
phenylalkylthioalkylene; wherein said phenylalkyl and

heterocyclcyl groups are optionally substituted with one or more radicals independently selected from lower alkyl and nitro; or

5         $R^{26}$  and  $R^{27}$  together with the nitrogen atom to which they are attached form a 4-8 membered ring heterocycle, wherein said heterocycle is optionally substituted with one or more radicals independently selected from lower alkyl, aryl selected from phenyl, biphenyl and naphthyl, heterocyclcyl, heterocyclcylalkylene, lower  
10 alkylheterocyclcylalkylene, lower phenoxyalkylene, lower alkoxyphenylene, lower alkylphenoxyalkylene, lower alkylcarbonyl, lower alkoxycarbonyl, lower phenylalkoxy carbonyl, lower alkylamino and lower alkoxy carbonylamino; wherein said aryl selected from  
15 phenyl, biphenyl and naphthyl, lower heterocyclcylalkylene and lower phenoxyalkylene radicals are optionally substituted with one or more radicals independently selected from halogen, lower alkyl and lower alkoxy; and  
       $R^2$  is selected from hydrido, halogen, lower alkyl, aryl selected from phenyl, biphenyl, and naphthyl, lower  
20 haloalkyl, lower hydroxyalkyl, 5- or 6-membered heterocyclcyl, lower alkylheterocyclcyl, lower heterocyclcylalkyl, lower alkylamino, lower alkynylamino, phenylamino, lower heterocyclcylamino, lower  
25 heterocyclcylalkylamino, lower phenylalkylamino, lower aminoalkyl, lower aminoalkylamino, lower alkylaminoalkylamino, lower cycloalkyl, lower alkenyl, lower alkoxy carbonylalkyl, lower cycloalkenyl, lower carboxyalkylamino, lower alkoxy carbonyl, lower  
30 heterocyclcylcarbonyl, lower alkoxy carbonylheterocyclcyl, lower alkoxy carbonylheterocyclcylcarbonyl, alkoxy carbonylalkyl, lower alkoxyalkylamino, lower alkoxy carbonylaminoalkylamino, lower heterocyclcylsulfonyl, lower heterocyclcylloxy, and lower  
35 heterocyclcylthio; wherein the aryl, heterocyclcyl, heterocyclcylalkyl, cycloalkyl, and cycloalkenyl groups

are optionally substituted with one or more radicals independently selected from halo, keto, lower alkyl, lower alkynyl, phenyl, 5- or 6-membered heterocyclyl, lower phenylalkyl, lower heterocyclylalkyl, lower epoxyalkyl, carboxy, lower alkoxy, lower aryloxy, lower phenylalkoxy, lower haloalkyl, lower alkylamino, lower alkylaminoalkylamino, lower alkynylamino, lower amino(hydroxyalkyl), lower heterocyclylalkylamino, lower alkylcarbonyl, lower alkoxy carbonyl, lower alkylsulfonyl, lower phenylalkylsulfonyl, and phenylsulfonyl; or

R<sup>2</sup> has the formula:



wherein:

j is 0, 1 or 2; and

m is 0;

R<sup>30</sup> and R<sup>31</sup> are independently selected from hydrogen, alkyl, aryl, heterocyclyl, aralkyl, heterocyclylalkylene, aminoalkyl, alkylaminoalkyl, aminocarbonylalkyl, alkoxyalkyl, and alkylcarbonyloxyalkyl; and

R<sup>32</sup> is selected from hydrogen, alkyl, aralkyl, heterocyclylalkyl, alkoxyalkylene, aryloxyalkylene, aminoalkyl, alkylaminoalkyl, arylaminoalkyl, alkylcarbonylalkylene, arylcarbonylalkylene, and heterocyclylcarbonylaminoalkylene; and

R<sup>33</sup> is selected from hydrogen, alkyl, -C(O)R<sup>35</sup>, -C(O)OR<sup>35</sup>, -SO<sub>2</sub>R<sup>36</sup>, -C(O)NR<sup>37</sup>R<sup>38</sup>, and -SO<sub>2</sub>NR<sup>39</sup>R<sup>40</sup>;

wherein R<sup>35</sup> is selected from alkyl, cycloalkyl, haloalkyl, alkenyl, aryl, heterocyclyl, aralkyl, arylcycloalkyl, cycloalkenylalkylene, heterocyclylalkylene, alkylarylene, alkylheterocyclyl, arylarylene, arylheterocyclyl, alkoxy, alkenoxy, alkoxyalkylene, alkoxyaralkyl, alkoxyarylene,

aryloxyalkylene, aralkoxyalkylene, cycloalkyloxyalkylene,  
alkoxycarbonyl, heterocyclylcarbonyl,  
alkylcarbonyloxyalkylene, alkylcarbonyloxyarylene,  
alkoxycarbonylalkylene, alkoxycarbonylarylene,  
5 aralkoxycarbonylheterocyclyl, alkylcarbonylheterocyclyl,  
arylcarbonyloxyalkylarylene, and alkylthioalkylene;  
wherein said aryl, heterocyclyl, aralkyl, alkylarylene,  
arylheterocyclyl, alkoxyarylene, aryloxyalkylene,  
cycloalkoxyalkylene, alkoxycarbonylalkylene, and  
10 alkylcarbonylheterocyclyl groups are optionally  
substituted with one or more radicals independently  
selected from alkyl, halo, haloalkyl, alkoxy, haloalkoxy,  
keto, amino, nitro, and cyano; or

$R^{35}$  is  $CHR^{48}R^{49}$  wherein  $R^{48}$  is arylsulfonylamino or  
15 alkylarylsulfonylamino, and  $R^{49}$  is selected from aralkyl,  
amino, alkylamino, and aralkylamino; or

$R^{35}$  is  $-NR^{50}R^{51}$  wherein  $R^{50}$  is alkyl, and  $R^{51}$  is aryl;  
and

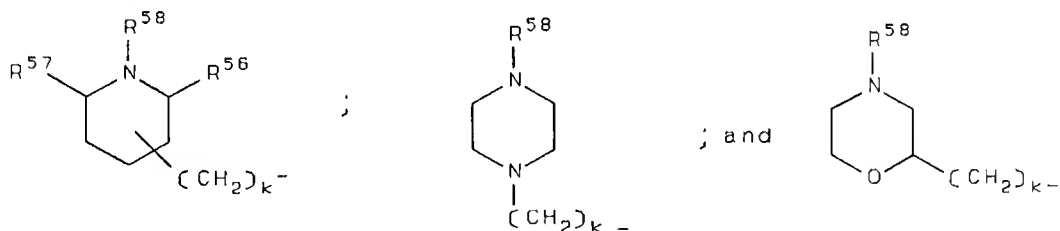
wherein  $R^{36}$  is selected from alkyl, haloalkyl, aryl,  
20 heterocyclyl, cycloalkylalkylene, alkylarylene,  
alkenylarylene, arylarylene, aralkyl, aralkenyl,  
heterocyclylheterocyclyl, carboxyarylene, alkoxyarylene,  
alkoxycarbonylarylene, alkylcarbonylaminoarylene,  
alkylcarbonylaminoheterocyclyl,  
25 arylcarbonylaminoalkylheterocyclyl, alkylaminoarylene,  
alkylamino, alkylaminoarylene, alkylsulfonylarylene,  
alkylsulfonylaralkyl, and arylsulfonylheterocyclyl;  
wherein said aryl, heterocyclyl, cycloalkylalkylene,  
aralkyl, alkylcarbonylaminoheterocyclyl, and  
30 alkylsulfonylarylene groups are optionally substituted  
with one or more radicals independently selected from  
alkyl, halo, hydroxy, haloalkyl, alkoxy, haloalkoxy,  
keto, amino, nitro, and cyano; and

wherein  $R^{37}$  is selected from hydrogen and alkyl; and

35 wherein  $R^{38}$  is selected from hydrogen, alkyl,  
alkenyl, aryl, heterocyclyl, aralkyl, alkylarylene,

arylcycloalkyl, arylarylene, cycloalkylalkylene,  
 heterocyclylalkylene, alkylheterocyclylalkylene,  
 aralkylheterocyclyl, alkoxyalkylene, alkoxyarylene,  
 aryloxyarylene, arylcarbonyl, alkoxycarbonyl,  
 5 alkoxycarbonylalkylene, alkoxycarbonylarylene,  
 alkylcarbonylcarbonylalkylene, alkylaminoalkylene,  
 alkylaminoaralkyl, alkylcarbonylaminoalkylene,  
 alkylthioarylene, alkylsulfonylaralkyl, and  
 aminosulfonylaralkyl; wherein said aryl, heterocyclyl,  
 10 aralkyl, and heterocyclylalkylene groups are optionally  
 substituted with one or more radicals independently  
 selected from alkyl, halo, hydroxy, haloalkyl, alkoxy,  
 haloalkoxy, keto, amino, nitro, and cyano; or  
 $R^{38}$  is  $-CR^{52}R^{53}$  wherein  $R^{52}$  is alkoxycarbonyl, and  $R^{53}$   
 15 is alkylthioalkylene; or  
 $R^{37}$  and  $R^{38}$  together with the nitrogen atom to which  
 they are attached form a heterocycle; and  
 $R^{39}$  and  $R^{40}$  have the same definition as  $R^{26}$  and  $R^{27}$  in  
 claim 1; or  
 20  $R^2$  is  $-CR^{54}R^{55}$  wherein  $R^{54}$  is phenyl and  $R^{55}$  is hydroxy;  
 or

$R^2$  is selected from the group consisting of



25 wherein  
 $k$  is an integer from 0 to 3; and  
 $R^{56}$  is hydrogen or lower alkyl; and  
 $R^{57}$  is hydrogen or lower alkyl; or  
 $R^{56}$  and  $R^{57}$  form a lower alkylene bridge; and

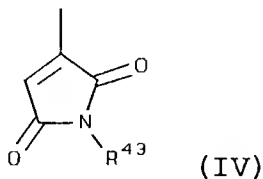
$R^{58}$  is selected from hydrogen, alkyl, aralkyl, aryl, heterocyclyl, heterocyclylalkyl, alkoxycarbonyl, alkylsulfonyl, aralkylsulfonyl, arylsulfonyl,  $-C(O)R^{59}$ ,  $-SO_2R^{60}$ , and  $-C(O)NHR^{61}$ ;

5        wherein  $R^{59}$  is selected from alkyl, haloalkyl, cycloalkyl, aryl, heterocyclyl, alkylarylene, aralkyl, alkylheterocyclyl, alkoxy, alkenoxy, aralkoxy, alkoxyalkylene, alkoxyarylene, alkoxyaralkyl; wherein said aryl, heterocyclyl, and aralkyl groups are  
10        optionally substituted with one or more radicals independently selected from alkyl, halo, hydroxy, haloalkyl, alkoxy, haloalkoxy, keto, amino, nitro, and cyano; and

          wherein  $R^{60}$  is selected from alkyl, aryl,  
15        heterocyclyl, alkylarylene, alkylheterocyclyl, aralkyl, heterocyclylheterocyclyl, alkoxyarylene, alkylamino, alkylaminoarylene, alkylsulfonylarylene, and arylsulfonylheterocyclyl; wherein said aryl, heterocyclyl, and aralkyl groups are optionally  
20        substituted with one or more radicals independently selected from alkyl, halo, hydroxy, haloalkyl, alkoxy, haloalkoxy, keto, amino, nitro, and cyano; and

          wherein  $R^{61}$  is selected from alkyl, aryl, alkylarylene, and alkoxyarylene; wherein said aryl group  
25        is optionally substituted with one or more radicals independently selected from alkyl, halo, hydroxy, haloalkyl, alkoxy, haloalkoxy, keto, amino, nitro, and cyano; and

$R^3$  is selected from pyridinyl, pyrimidinyl,  
30        quinolinyl, purinyl, and







A class of compounds of particular interest consists of these compounds of Formula I wherein

R<sup>1</sup> is selected from hydrido, methyl, ethyl, propyl, isopropyl, tert-butyl, isobutyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloroethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, ethenyl, propenyl, ethynyl, propargyl, 1-propynyl, 2-propynyl, piperidinyl, piperazinyl, morpholinyl, benzyl, phenylethyl, morpholinylmethyl, morpholinylethyl, pyrrolidinylmethyl, piperazinylmethyl, piperidinylmethyl, pyridinylmethyl, thienylmethyl, methoxymethyl, ethoxymethyl, amino, methylamino, dimethylamino, phenylamino, methylaminomethyl, dimethylaminomethyl, methylaminoethyl, dimethylaminoethyl, ethylaminoethyl, diethylaminoethyl, cyclopropyl, cyclopentyl, cyclohexyl, cyclohexylmethyl, hydroxymethyl, hydroxyethyl, mercaptomethyl, and methylthiomethyl; and

R<sup>2</sup> is selected from hydrido, chloro, fluoro, bromo, methyl, ethyl, propyl, isopropyl, tert-butyl, isobutyl, phenyl, biphenyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxymethyl, hydroxyethyl, pyridinyl, isothiazolyl, isoxazolyl, thienyl, thiazolyl, oxazolyl, pyrimidinyl, quinolyl, isoquinolinyl, imidazolyl, benzimidazolyl, furyl, pyrazinyl, piperidinyl, piperazinyl, morpholinyl, N-methylpiperazinyl, methoxycarbonylethyl, ethoxycarbonylethyl, N-methylamino, N,N-dimethylamino, N-ethylamino, N,N-diethylamino, N-n-propylamino, N,N-dimethylamino, N-methyl-N-phenylamino, N-phenylamino, piperadinylamino, N-benzylamino, N-

propargylamino, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, aminomethyl, aminoethyl, aminoethylamino, aminopropylamino, N,N-

5 dimethylaminoethylamino, N,N-dimethylaminopropylamino, morpholinylethylamino, morpholinylpropylamino, carboxymethylamino, methoxyethylamino, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, 1,1-

10 dimethylethoxycarbonyl, 1,1-dimethylethoxycarbonylaminoethylamino, 1,1-dimethylethoxycarbonylaminopropylamino, piperazinylcarbonyl, and 1,1-

15 dimethylethoxycarbonylpiperazinylcarbonyl; wherein the aryl, heteroaryl, cycloalkyl and cycloalkenyl groups are optionally substituted with one or more radicals

independently selected from fluoro, chloro, bromo, keto, methyl, ethyl, isopropyl, tert-butyl, isobutyl, benzyl, carboxy, methoxy, ethoxy, phenoxy, benzyloxy, trifluoromethyl, fluoromethyl, difluoromethyl,

20 dimethylamino, methoxycarbonyl, ethoxycarbonyl, and 1,1-dimethylethylcarbonyl; or

$R^2$  is  $-CR^{54}R^{55}$  wherein  $R^{54}$  is phenyl and  $R^{55}$  is hydroxy; and

$R^3$  is selected from pyridinyl, pyrimidinyl, and

25 purinyl; wherein  $R^3$  is optionally substituted with one or more radicals independently selected from methylthio, methylsulfinyl, methylsulfonyl, fluoro, chloro, bromo, aminosulfonyl, methyl, ethyl, isopropyl, tert-butyl, isobutyl, cyano, methoxycarbonyl, ethoxycarbonyl,

30 aminocarbonyl, methylcarbonylamino, trifluoromethyl, difluoromethyl, fluoromethyl, trichloromethyl, dichloromethyl, chloromethyl, hydroxy, fluorophenylmethyl, fluorophenylethyl, chlorophenylmethyl, chlorophenylethyl,

35 fluorophenylethenyl, chlorophenylethenyl, fluorophenylpyrazolyl, chlorophenylpyrazolyl, carboxy,

methoxy, ethoxy, propyloxy, n-butoxy, methylamino, ethylamino, dimethylamino, diethylamino, 2-methylbutylamino, propargylamino, aminomethyl, aminoethyl, N-methyl-N-phenylamino, phenylamino, 5 diphenylamino, benzylamino, phenethylamino, cyclopropylamino, nitro, chlorosulfonyl, amino, methylcarbonyl, methoxycarbonylamino, ethoxycarbonylamino, methoxyphenylmethylamino, N,N-dimethylaminoethylamino, hydroxypropylamino, 10 hydroxyethylamino, imidazolylethylamino, morpholinylethylamino, (1-ethyl-2-hydroxy)ethylamino, piperidinylamino, pyridinylmethylamino, phenylmethylpiperidinylamino, phenylmethylamino, fluorophenylmethylamino, fluorophenylethylamino, 15 methylaminocarbonyl, ethylaminocarbonyl, methylcarbonyl, methoxyphenylmethylamino, hydrazinyl, 1-methylhydrazinyl, or  $-NR^{62}R^{63}$  wherein  $R^{62}$  is methylcarbonyl or amino, and  $R^{63}$  is methyl, ethyl or phenylmethyl; and  $R^4$  is selected from hydrido, cyclopropyl, cyclobutyl, 20 cyclopentyl, cyclohexyl, cyclopropylenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, phenyl, biphenyl, morpholinyl, pyrrolidinyl, piperazinyl, piperidinyl, pyridinyl, thienyl, isothiazolyl, isoxazolyl, thiazolyl, oxazolyl, pyrimidinyl, quinolyl, 25 isoquinolinyl, imidazolyl, benzimidazolyl, furyl, pyrazinyl, dihydropyranyl, dihydropyridinyl, dihydrofuryl, tetrahydropyranyl, tetrahydrofuryl, benzofuryl, dihydrobenzofuryl, and benzodioxolyl; wherein the cycloalkyl, cycloalkenyl, aryl and heterocyclyl 30 groups of  $R^4$  are optionally substituted with one or more radicals independently selected from methylthio, methylsulfinyl, methylsulfonyl, fluoro, chloro, bromo, methyl, ethyl, isopropyl, tert-butyl, isobutyl, ethynyl, methoxy, ethoxy, phenoxy, benzyloxy, trifluoromethyl, 35 fluoromethyl, difluoromethyl, amino, cyano, nitro, dimethylamino, and hydroxy; or

a pharmaceutically-acceptable salt or tautomer thereof.

Another class of compounds of particular interest  
5 consists of these compounds of Formula I wherein

R<sup>1</sup> is hydrido, methyl, ethyl, propargyl, hydroxyethyl, dimethylaminoethyl, diethylaminoethyl or morpholinylethyl;

R<sup>2</sup> is selected from hydrido, methyl, ethyl, propyl,  
10 phenyl, trifluoromethyl, methoxycarbonylethyl, N,N-dimethylamino, N-phenylamino, piperidinyl, piperazinyl, pyridinyl, N-methylpiperazinyl, and piperazinylamino; wherein the phenyl, piperidinyl, and pyridinyl groups are optionally substituted with one or more radicals  
15 independently selected from fluoro, chloro, bromo, methyl, ethyl, and trifluoromethyl;

R<sup>3</sup> is selected from pyridinyl, pyrimidinyl or quinolinyl; wherein R<sup>3</sup> is optionally substituted with one or more radicals independently selected from fluoro,  
20 bromo, methyl, cyano, methoxycarbonyl, aminocarbonyl, benzyl, phenethyl, acetyl, hydroxyl, methoxy, dimethylamino, benzylamino, phenethylamino, aminomethyl, amino, hydroxy, and methylcarbonyl;

R<sup>4</sup> is selected from phenyl, quinolyl, biphenyl,  
25 pyridinyl, thienyl, furyl, dihydropyranyl, benzofuryl, dihydrobenzofuryl, and benzodioxolyl; wherein the cycloalkyl, cycloalkenyl, aryl and heterocyclyl groups of R<sup>4</sup> are optionally substituted with one or more radicals independently selected from methylthio, fluoro, chloro,  
30 bromo, methyl, ethyl, methoxy, ethoxy, phenoxy, benzyloxy, trifluoromethyl, nitro, dimethylamino, and hydroxy; or

a pharmaceutically-acceptable salt or tautomer thereof.

35

A class of compounds of specific interest consists

of those compounds of Formula I wherein

R<sup>1</sup> is hydrido or methyl;

R<sup>2</sup> is selected from hydrido, methyl or ethyl;

R<sup>3</sup> is selected from pyridinyl, pyrimidinyl or  
5 quinolinyl; wherein R<sup>3</sup> is optionally substituted with one  
or more radicals independently selected from fluoro,  
bromo, methyl, cyano, methoxycarbonyl, aminocarbonyl,  
benzyl, phenethyl, acetyl, hydroxyl, methoxy,  
dimethylamino, benzylamino, phenethylamino, aminomethyl,  
10 amino, hydroxy, and methylcarbonyl;

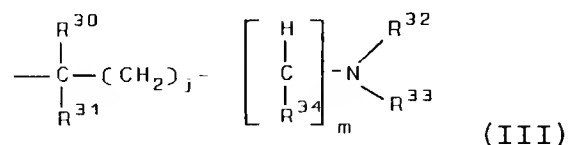
R<sup>4</sup> is selected from phenyl which is optionally  
substituted with one or more radicals independently  
selected from methylthio, fluoro, chloro, bromo, methyl,  
ethyl, methoxy, ethoxy, phenoxy, benzyloxy,  
15 trifluoromethyl, nitro, dimethylamino, and hydroxy; or  
a pharmaceutically-acceptable salt or tautomer  
thereof.

Still another class of compounds of particular  
20 interest consists of those compounds of Formula I wherein

R<sup>1</sup> is selected from hydrido, methyl, ethyl, propyl,  
isopropyl, tert-butyl, isobutyl, fluoromethyl,  
difluoromethyl, trifluoromethyl, chloromethyl,  
dichloromethyl, trichloroethyl, pentafluoroethyl,  
25 heptafluoropropyl, difluorochloromethyl,  
dichlorofluoromethyl, difluoroethyl, difluoropropyl,  
dichloroethyl, dichloropropyl, ethenyl, propenyl,  
ethynyl, propargyl, 1-propynyl, 2-propynyl, piperidinyl,  
piperazinyl, morpholinyl, benzyl, phenylethyl,  
30 morpholinylmethyl, morpholinylethyl, pyrrolidinylmethyl,  
piperazinylmethyl, piperidinylmethyl, pyridinylmethyl,  
thienylmethyl, methoxymethyl, ethoxymethyl, amino,  
methylamino, dimethylamino, phenylamino,  
methylaminomethyl, dimethylaminomethyl, methylaminoethyl,  
35 dimethylaminoethyl, ethylaminoethyl, diethylaminoethyl,  
cyclopropyl, cyclopentyl, cyclohexyl, cyclohexylmethyl,

hydroxymethyl, hydroxyethyl, mercaptomethyl, and methylthiomethyl; and

R<sup>2</sup> has the formula:



5           wherein:

j is 0, 1 or 2; and

m is 0; and

R<sup>30</sup> and R<sup>31</sup> are independently selected from hydrogen and lower alkyl;

10           R<sup>32</sup> is selected from hydrogen, lower alkyl, lower phenylalkyl, lower heterocyclalkyl, lower alkoxyalkylene, aryloxyalkylene, aminoalkyl, lower alkylaminoalkyl, lower phenylaminoalkyl, lower alkylcarbonylalkylene, lower phenylcarbonylalkylene, and  
15 lower heterocyclcarbonylaminoalkylene;

R<sup>33</sup> is selected from hydrogen, lower alkyl, -C(O)R<sup>35</sup>, -C(O)OR<sup>35</sup>, -SO<sub>2</sub>R<sup>36</sup>, -C(O)NR<sup>37</sup>R<sup>38</sup>, and -SO<sub>2</sub>NR<sup>39</sup>R<sup>40</sup>;

wherein R<sup>35</sup> is selected from lower alkyl, lower cycloalkyl, lower haloalkyl, lower alkenyl, aryl selected  
20 from phenyl, biphenyl and naphthyl, lower heterocycl, lower phenylalkyl, lower phenylcycloalkyl, lower cycloalkenylalkylene, lower heterocyclalkylene, lower alkylphenylene, lower alkylheterocycl, phenylphenylene, lower phenylheterocycl, lower alkoxy, lower alkenoxy,  
25 lower alkoxyalkylene, lower alkoxyphenylalkyl, lower alkoxyphenylene, lower phenoxyalkylene, lower phenylalkoxyalkylene, lower cycloalkyloxyalkylene, lower alkoxycarbonyl, lower heterocyclcarbonyl, lower alkylcarbonyloxyalkylene, lower  
30 alkylcarbonyloxyphenylene, lower alkoxycarbonylalkylene, lower alkoxycarbonylphenylene, lower phenylalkoxycarbonylheterocycl, lower

alkylcarbonylheterocyclyl, lower  
phenylcarbonyloxyalkylphenylene, and lower  
alkylthioalkylene; wherein said aryl selected from  
phenyl, biphenyl and naphthyl, lower heterocyclyl, lower  
5 phenylalkyl, lower alkylphenylene, lower  
phenylheterocyclyl, lower alkoxyphenylene, lower  
phenoxyalkylene, lower cycloalkoxyalkylene, lower  
alkoxycarbonylalkylene, and lower  
alkylcarbonylheterocyclyl groups are optionally  
10 substituted with one or more radicals independently  
selected from lower alkyl, halo, lower haloalkyl, lower  
alkoxy, lower haloalkoxy, keto, amino, nitro, and cyano;  
or

$R^{35}$  is  $CHR^{48}R^{49}$  wherein  $R^{48}$  is phenylsulfonylamino or  
15 lower alkylphenylsulfonylamino, and  $R^{49}$  is selected from  
lower phenylalkyl, amino, lower alkylamino, and lower  
phenylalkylamino; or

$R^{35}$  is  $-NR^{50}R^{51}$  wherein  $R^{50}$  is lower alkyl, and  $R^{51}$  is  
aryl selected from phenyl, biphenyl and naphthyl; and  
20 wherein  $R^{36}$  is selected from lower alkyl, lower  
haloalkyl, aryl selected from phenyl, biphenyl and  
naphthyl, lower heterocyclyl, lower cycloalkylalkylene,  
lower alkylphenylene, lower alkenylphenylene,  
phenylphenylene, lower phenylalkyl, lower phenylalkenyl,  
25 lower heterocyclylheterocyclyl, carboxyphenylene, lower  
alkoxyphenylene, lower alkoxycarbonylphenylene, lower  
alkylcarbonylaminophenylene, lower  
alkylcarbonylaminoheterocyclyl, lower  
phenylcarbonylaminoalkylheterocyclyl, lower  
30 alkylaminophenylene, lower alkylamino, lower  
alkylaminophenylene, lower alkylsulfonylphenylene, lower  
alkylsulfonylphenylalkyl, and lower  
phenylsulfonylheterocyclyl; wherein said aryl selected  
from phenyl, biphenyl and naphthyl, lower heterocyclyl,  
35 lower cycloalkylalkylene, lower phenylalkyl, lower  
alkylcarbonylaminoheterocyclyl, and lower



alkylsulfonylphenylene groups are optionally substituted with one or more radicals independently selected from lower alkyl, halo, hydroxy, lower haloalkyl, lower alkoxy, lower haloalkoxy, keto, amino, nitro, and cyano; and

wherein  $R^{37}$  is selected from hydrogen and lower alkyl; and

wherein  $R^{38}$  is selected from hydrogen, lower alkyl, lower alkenyl, aryl selected from phenyl, biphenyl and naphthyl, lower heterocyclyl, lower phenylalkyl, lower alkylphenylene, lower phenylcycloalkyl, phenylphenylene, lower cycloalkylalkylene, lower heterocyclylalkylene, lower alkylheterocyclylalkylene, lower phenylalkylheterocyclyl, lower alkoxyalkylene, lower alkoxyphenylene, lower phenoxyphenylene, phenylcarbonyl, lower alkoxy carbonyl, lower alkoxy carbonylalkylene, lower alkoxy carbonylphenylene, lower alkylcarbonylcarbonylalkylene, lower alkylaminoalkylene, lower alkylaminophenylalkyl, lower alkylcarbonylaminoalkylene, lower alkylthiophenylene, lower alkylsulfonylphenylalkyl, and lower aminosulfonylphenylalkyl; wherein said aryl selected from phenyl, biphenyl and naphthyl, lower heterocyclyl, lower phenylalkyl, and lower heterocyclylalkylene groups are optionally substituted with one or more radicals independently selected from lower alkyl, halo, hydroxy, lower haloalkyl, lower alkoxy, lower haloalkoxy, keto, amino, nitro, and cyano; or

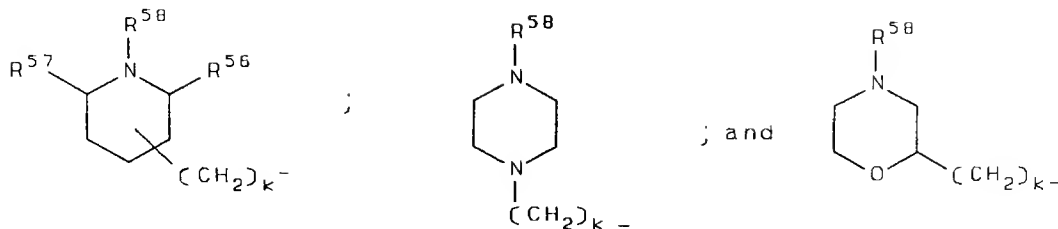
$R^{38}$  is  $-CR^{52}R^{53}$  wherein  $R_{52}$  is lower alkoxy carbonyl, and  $R_{53}$  is lower alkylthioalkylene; or

$R^{37}$  and  $R^{38}$  together with the nitrogen atom to which they are attached form a 4-8 membered ring heterocycle;

$R^{39}$  and  $R^{40}$  have the same definition as  $R^{26}$  and  $R^{27}$  in claim 2; or

$R^2$  is selected from the group consisting of

43



(VI)

(VII)

(VIII)

wherein

k is an integer from 0 to 2; and

5 R<sup>56</sup> is hydrogen or lower alkyl; andR<sup>57</sup> is hydrogen or lower alkyl; and

10 R<sup>58</sup> is selected from hydrogen, lower alkyl, lower phenylalkyl, aryl selected from phenyl, biphenyl and naphthyl, lower heterocyclyl, lower heterocyclylalkyl, lower alkoxy carbonyl, lower alkylsulfonyl, lower phenylalkylsulfonyl, lower phenylsulfonyl, -C(O)R<sup>59</sup>, -SO<sub>2</sub>R<sup>60</sup>, and -C(O)NHR<sup>61</sup>;

15 wherein R<sup>59</sup> is selected from lower alkyl, lower haloalkyl, lower cycloalkyl, aryl selected from phenyl, biphenyl and naphthyl, lower heterocyclyl, lower alkylphenylene, lower phenylalkyl, lower alkylheterocyclyl, lower alkoxy, lower alkenoxy, lower phenylalkoxy, lower alkoxyalkylene, lower alkoxyphenylene, lower alkoxyphenylalkyl; wherein said  
 20 aryl selected from phenyl, biphenyl and naphthyl, lower heterocyclyl, and lower phenylalkyl groups are optionally substituted with one or more radicals independently selected from lower alkyl, halo, hydroxy, lower haloalkyl, lower alkoxy, lower haloalkoxy, keto, amino,  
 25 nitro, and cyano; and

wherein R<sup>60</sup> is selected from lower alkyl, aryl selected from phenyl, biphenyl and naphthyl, lower heterocyclyl, lower alkylphenylene, lower alkylheterocyclyl, lower phenylalkyl, lower

heterocyclylheterocyclyl, lower alkoxyphenylene, lower  
alkylamino, lower alkylaminophenylene, lower  
alkylsulfonylphenylene, and lower  
phenylsulfonylheterocyclyl; wherein said aryl selected  
5 from phenyl, biphenyl and naphthyl, lower heterocyclyl,  
and lower phenylalkyl groups are optionally substituted  
with one or more radicals independently selected from  
lower alkyl, halo, hydroxy, lower haloalkyl, lower  
alkoxy, lower haloalkoxy, keto, amino, nitro, and cyano;  
10 and

wherein R<sup>61</sup> is selected from lower alkyl, aryl  
selected from phenyl, biphenyl and naphthyl, lower  
alkylphenylene, and lower alkoxyphenylene; wherein said  
aryl group is optionally substituted with one or more  
15 radicals independently selected from lower alkyl, halo,  
hydroxy, lower haloalkyl, lower alkoxy, lower haloalkoxy,  
keto, amino, nitro, and cyano; and

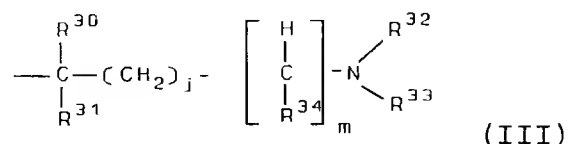
R<sup>3</sup> is selected from pyridinyl, pyrimidinyl, and  
purinyl; wherein R<sup>3</sup> is optionally substituted with one or  
20 more radicals independently selected from methylthio,  
methylsulfinyl, methylsulfonyl, fluoro, chloro, bromo,  
aminosulfonyl, methyl, ethyl, isopropyl, tert-butyl,  
isobutyl, cyano, methoxycarbonyl, ethoxycarbonyl,  
aminocarbonyl, methylcarbonylamino, trifluoromethyl,  
25 difluoromethyl, fluoromethyl, trichloromethyl,  
dichloromethyl, chloromethyl, hydroxy,  
fluorophenylmethyl, fluorophenylethyl,  
chlorophenylmethyl, chlorophenylethyl,  
fluorophenylethenyl, chlorophenylethenyl,  
30 fluorophenylpyrazolyl, chlorophenylpyrazolyl, carboxy,  
methoxy, ethoxy, propyloxy, n-butoxy, methylamino,  
ethylamino, dimethylamino, diethylamino, 2-  
methylbutylamino, propargylamino, aminomethyl,  
aminoethyl, N-methyl-N-phenylamino, phenylamino,  
35 diphenylamino, benzylamino, phenethylamino,  
cyclopropylamino, nitro, chlorosulfonyl, amino,

methylcarbonyl, methoxycarbonylamino, ethoxycarbonylamino, methoxyphenylmethylamino, N,N-dimethylaminoethylamino, hydroxypropylamino, hydroxyethylamino, imidazolylethylamino, morpholinylethylamino, (1-ethyl-2-hydroxy)ethylamino, piperidinylamino, pyridinylmethylamino, phenylmethylpiperidinylamino, phenylmethylamino, fluorophenylmethylamino, fluorophenylethylamino, methylaminocarbonyl, ethylaminocarbonyl, methylcarbonyl, methoxyphenylmethylamino, hydrazinyl, 1-methyl-hydrazinyl, or  $-NR^{62}R^{63}$  wherein  $R^{62}$  is methylcarbonyl or amino, and  $R^{63}$  is methyl, ethyl or phenylmethyl; and  $R^4$  is selected from hydrido, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, phenyl, biphenyl, morpholinyl, pyrrolidinyl, piperazinyl, piperidinyl, pyridinyl, thienyl, isothiazolyl, isoxazolyl, thiazolyl, oxazolyl, pyrimidinyl, quinolyl, isoquinolinyl, imidazolyl, benzimidazolyl, furyl, pyrazinyl, dihydropyranyl, dihydropyridinyl, dihydrofuryl, tetrahydropyranyl, tetrahydrofuryl, benzofuryl, dihydrobenzofuryl, and benzodioxolyl; wherein the cycloalkyl, cycloalkenyl, aryl and heterocyclyl groups of  $R^4$  are optionally substituted with one or more radicals independently selected from methylthio, methylsulfinyl, methylsulfonyl, fluoro, chloro, bromo, methyl, ethyl, isopropyl, tert-butyl, isobutyl, ethynyl, methoxy, ethoxy, phenoxy, benzyloxy, trifluoromethyl, fluoromethyl, difluoromethyl, amino, cyano, nitro, dimethylamino, and hydroxy; or a pharmaceutically-acceptable salt or tautomer thereof.

Still another class of compounds of particular interest consists of those compounds of Formula I wherein  $R^1$  is hydrido, methyl, ethyl, propargyl,

hydroxyethyl, dimethylaminoethyl, diethylaminoethyl or morpholinylethyl;

R<sup>2</sup> has the formula:



5           wherein:

j is 0, 1 or 2; and

m is 0; and

R<sup>30</sup> is hydrogen; and

R<sup>31</sup> is selected from hydrogen and lower alkyl; and

10          R<sup>32</sup> is selected from hydrogen and lower alkyl; and

R<sup>33</sup> is selected from lower alkyl, -C(O)R<sup>35</sup>, -C(O)OR<sup>35</sup>,  
-SO<sub>2</sub>R<sup>36</sup>, -C(O)NR<sup>37</sup>R<sup>38</sup>, and -SO<sub>2</sub>NR<sup>39</sup>R<sup>40</sup>;

wherein R<sup>35</sup> is selected from lower alkyl, lower  
cycloalkyl, phenyl, lower heterocyclyl, lower  
15   alkylphenylene, lower alkoxy, lower alkenoxy, lower  
alkoxyalkylene, lower phenoxyalkylene, and lower  
phenylalkoxyalkylene; wherein said phenyl and lower  
phenoxyalkylene groups are optionally substituted with  
one or more radicals independently selected from lower  
20   alkyl, halo, and lower haloalkyl; and

wherein R<sup>36</sup> is selected from lower alkyl, phenyl,  
lower heterocyclyl, lower alkylphenylene,  
phenylphenylene, lower phenylalkyl, lower  
alkylheterocyclyl, lower heterocyclylheterocyclyl, lower  
25   alkoxyphenylene, and lower alkylamino; wherein said  
phenyl and lower heterocyclyl groups are optionally  
substituted with one or more radicals independently  
selected from lower alkyl, halo, hydroxy, lower  
haloalkyl, lower alkoxy, lower haloalkoxy, keto, amino,  
30   nitro, and cyano; and

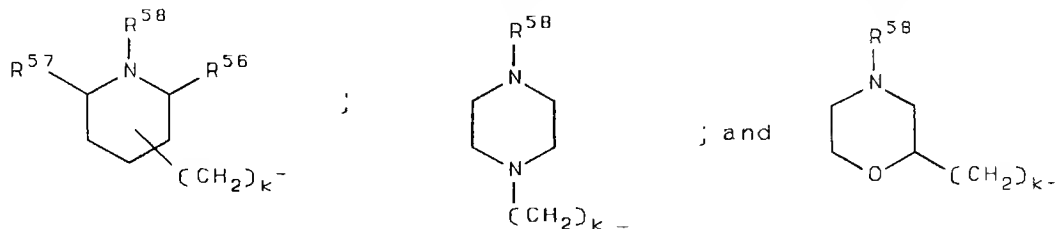
wherein R<sup>37</sup> is hydrogen; and

wherein R<sup>38</sup> is selected from lower alkyl, phenyl, and

lower alkylphenylene;

wherein  $R^{39}$  and  $R^{40}$  have the same definition as  $R^{26}$  and  $R^{27}$  in claim 2; or

$R^2$  is selected from the group consisting of



wherein

$k$  is an integer from 0 or 1; and

$R^{56}$  is hydrogen; and

10  $R^{57}$  is hydrogen; and

$R^{58}$  is selected from  $-C(O)R^{59}$  and  $-SO_2R^{60}$ ;

wherein  $R^{59}$  is selected from lower alkyl, lower cycloalkyl, phenyl, lower alkylphenylene, and lower alkoxyalkylene; wherein said phenyl group is optionally  
 15 substituted with one or more radicals independently selected from lower alkyl, halo, hydroxy, lower haloalkyl, lower alkoxy, lower haloalkoxy, keto, amino, nitro, and cyano; and

wherein  $R^{60}$  is selected from lower alkyl; and

20  $R^3$  is selected from pyridinyl, pyrimidinyl or quinolinyl; wherein  $R^3$  is optionally substituted with one or more radicals independently selected from fluoro, bromo, methyl, cyano, methoxycarbonyl, aminocarbonyl, benzyl, phenethyl, acetyl, hydroxyl, methoxy, dimethylamino, benzylamino, phenethylamino, aminomethyl,  
 25 amino, hydroxy, and methylcarbonyl; and

$R^4$  is selected from phenyl, quinolyl, biphenyl, pyridinyl, thienyl, furyl, dihydropyranyl, benzofuryl, dihydrobenzofuryl, and benzodioxolyl; wherein the

cycloalkyl, cycloalkenyl, aryl and heterocyclyl groups of  $R^4$  are optionally substituted with one or more radicals independently selected from methylthio, fluoro, chloro, bromo, methyl, ethyl, methoxy, ethoxy, phenoxy, benzyloxy, trifluoromethyl, nitro, dimethylamino, and hydroxy; or  
a pharmaceutically-acceptable salt or tautomer thereof.

Still another class of compounds of specific interest consists of those compounds of Formula I wherein  $R^1$  is hydrido or methyl; and  $R^3$  is selected from pyridinyl, pyrimidinyl or quinolinyl; wherein  $R^3$  is optionally substituted with one or more radicals independently selected from fluoro, bromo, methyl, cyano, methoxycarbonyl, aminocarbonyl, benzyl, phenethyl, acetyl, hydroxyl, methoxy, dimethylamino, benzylamino, phenethylamino, aminomethyl, amino, hydroxy, and methylcarbonyl; and  $R^4$  is selected from phenyl which is optionally substituted with one or more radicals independently selected from methylthio, fluoro, chloro, bromo, methyl, ethyl, methoxy, ethoxy, phenoxy, benzyloxy, trifluoromethyl, nitro, dimethylamino, and hydroxy; or a pharmaceutically-acceptable salt or tautomer thereof.

In one embodiment of the present invention, the compounds of Formula I and/or 1A satisfy one or more of the following conditions:

$R^1$  is hydrido or lower alkyl; more preferably,  $R^1$  is hydrido or methyl; and still more preferably,  $R^1$  is hydrido;  
 $R^2$  is hydrido or lower alkyl; more preferably,  $R^2$  is hydrido or methyl; and still more preferably,  $R^2$  is hydrido;

R<sup>2</sup> comprises a piperidinyl, piperazinyl or cyclohexyl moiety;

R<sup>3</sup> is substituted or unsubstituted pyridinyl; and preferably, the pyridinyl is a 4-pyridinyl; or

5 R<sup>4</sup> is substituted or unsubstituted phenyl; and preferably, R<sup>4</sup> is phenyl substituted with halo.

In addition, where R<sup>3</sup> is substituted pyrimidinyl, preferably at least one R<sup>3</sup> substituent is attached to the carbon atom positioned between two nitrogen atoms of the  
10 pyrimidinyl ring.

A family of specific compounds of particular interest within Formula I and/or 1A consists of compounds, tautomers and pharmaceutically-acceptable  
15 salts thereof as follows:

4-[5-(3-fluoro-4-methoxyphenyl)-3-methyl-1H-pyrazol-4-yl]pyridine;  
4-(3-methyl-5-phenyl-1H-pyrazol-4-yl)pyridine;  
4-[5-methyl-3-(2-methylphenyl)-1H-pyrazol-4-yl]pyridine;  
20 4-[3-(4-fluorophenyl)-5-methyl-1H-pyrazol-4-yl]pyridine;  
4-[5-methyl-3-(4-methylphenyl)-1H-pyrazol-4-yl]pyridine;  
4-[5-methyl-3-[4-(methylthio)phenyl]-1H-pyrazol-4-yl]pyridine;  
4-[3-(4-chlorophenyl)-5-methyl-1H-pyrazol-4-yl]pyridine;  
25 4-[3-methyl-5-(3-methylphenyl)-1H-pyrazol-4-yl]pyridine;  
4-[5-(2,5-dimethylphenyl)-3-methyl-1H-pyrazol-4-yl]pyridine;  
4-[5-(1,3-benzodioxol-5-yl)-3-methyl-1H-pyrazol-4-yl]pyridine;  
30 4-[3-methyl-5-(4-phenoxyphenyl)-1H-pyrazol-4-yl]pyridine;  
4-[5-[(1,1'-biphenyl)-4-yl]-3-methyl-1H-pyrazol-4-yl]pyridine;  
4-[3-methyl-5-[3-(phenoxyphenyl)-1H-pyrazol-4-yl]pyridine;  
35 4-[3-methyl-5-[3-(phenylmethoxy)phenyl]-1H-pyrazol-4-yl]pyridine;



4-[3-methyl-5-[2-(phenylmethoxy)phenyl]-1H-pyrazol-4-yl]pyridine;  
2-[3-methyl-4-(4-pyridinyl)-1H-pyrazol-4-yl]phenol;  
3-[3-methyl-4-(4-pyridinyl)-1H-pyrazol-4-yl]phenol;  
5 1-hydroxy-4-(3-methyl-5-phenyl-1H-pyrazol-4-yl)pyridinium;  
5-(4-fluorophenyl)-N,N-dimethyl-4-(4-pyridinyl)-1H-pyrazol-3-amine;  
5-(4-fluorophenyl)-N-phenyl-4-(4-pyridinyl)-1H-pyrazol-3-amine;  
10 4-[5-(4-fluorophenyl)-3-phenyl-1H-pyrazol-4-yl]pyridine;  
4-[5-(3-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl]pyridine;  
4-[3-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-5-yl]pyridine;  
15 4-(5-cyclohexyl)-3-methyl-1H-pyrazol-4-yl]pyridine;  
4-[5-(3-fluoro-5-methoxyphenyl)-3-methyl-1H-pyrazol-4-yl]pyridine;  
4-[5-(3-methylphenyl)-3-propyl-1H-pyrazol-4-yl]pyridine;  
4-[(3-methyl-5-phenyl-1H-pyrazol-4-yl)methyl]pyridine;  
20 4-[3,5-bis(3-methylphenyl)-1H-pyrazol-4-yl]pyridine;  
4-[4-methyl-2-(2-trifluorophenyl)-1H-pyrazol-4-yl]pyridine;  
4-[3-(2-chlorophenyl)-5-methyl-1H-pyrazol-4-yl]pyridine;  
4-[5-methyl-3-(2,4-dimethylphenyl)-1H-pyrazol-4-yl]pyridine;  
25 4-[5-(4-chlorophenyl)-1,3-dimethyl-1H-pyrazol-4-yl]pyridine;  
4-[3-(3-fluoro-2-methylphenyl)-5-methyl-1H-pyrazol-4-yl]pyridine;  
30 4-[3-(3,5-dimethylphenyl)-5-methyl-1H-pyrazol-4-yl]pyridine;  
4-[3-(3,5-dimethoxyphenyl)-5-methyl-1H-pyrazol-4-yl]pyridine;  
4-[5-methyl-3-(3-nitrophenyl)-1H-pyrazol-4-yl]pyridine;  
35 N,N-dimethyl-4-[5-methyl-4-(4-pyridinyl)-1H-pyrazol-3-yl]benzenamine;

- 4- [3- (2,3-dihydrobenzofuran-5-yl) -5-methyl-1H-pyrazol-4-yl]pyridine;  
4- [3- (4-bromophenyl) -5-methyl-1H-pyrazol-4-yl]pyridine;  
4- [3- (2-fluorophenyl) -5-methyl-1H-pyrazol-4-yl]pyridine;  
5 4- [3- (3-fluorophenyl) -5-methyl-1H-pyrazol-4-yl]pyridine;  
4- [3-methyl-5- [3- (trifluoromethyl) phenyl] -1H-pyrazol-4-yl]pyridine;  
4- (3-ethyl-4-phenyl-1H-pyrazol-4-yl)pyridine;  
4- [5- (3-methoxyphenyl) -3-methyl-1H-pyrazol-4-yl]pyridine;  
10 4- [3-ethyl-5- (3-methylphenyl) -1H-pyrazol-4-yl]pyridine;  
4- [5- (3,4-difluorophenyl) -3-methyl-1H-pyrazol-4-yl]pyridine;  
4- [5- (3-ethoxyphenyl) -3-methyl-1H-pyrazol-4-yl]pyridine;  
4- [3-methyl-5- [4- (trifluoromethyl) phenyl] -1H-pyrazol-4-yl]pyridine;  
15 4- [3-methyl-5- (3-thienyl) -1H-pyrazol-4-yl]pyridine;  
4- [5- (2,4-dichlorophenyl) -3-methyl-1H-pyrazol-4-yl]pyridine;  
4- [5- (3-chlorophenyl) -3-methyl-1H-pyrazol-4-yl]pyridine;  
20 4- [5- (3-chloro-4-methoxyphenyl) -3-methyl-1H-pyrazol-4-yl]pyridine;  
ethyl 3- (4-chlorophenyl) -4- (4-pyridinyl) -1H-pyrazole-5-propanoate;  
4- [3- (4-fluorophenyl) -1-methyl-pyrazol-4-yl]pyridine;  
25 5- [5- (3-chlorophenyl) -3-methyl-1H-pyrazol-4-yl]pyrimidin-2-amine;  
5- [3-methyl-5- (3-methylphenyl) -1H-pyrazol-4-yl]pyrimidin-2-amine;  
5- [3-methyl-5- (2-methylphenyl) -1H-pyrazol-4-yl]pyrimidin-2-amine;  
30 5- [5- (4-chlorophenyl) -3-methyl-1H-pyrazol-4-yl]pyrimidin-2-amine;  
5- [5- (4-fluorophenyl) -3-methyl-1H-pyrazol-4-yl]pyrimidin-2-amine;  
35 5- [5- (4-methoxyphenyl) -3-methyl-1H-pyrazol-4-yl]pyrimidin-2-amine;

- 5- [5- (3-chlorophenyl) -3-methyl-1H-pyrazol-4-yl]pyridin-2-amine;
- 4- [5- (3-chlorophenyl) -3-methyl-1H-pyrazol-4-yl]pyridin-2-amine;
- 5 4- [5- (3-methylphenyl) -3-methyl-1H-pyrazol-4-yl]pyridin-2-amine;
- 4- [5- (2-methylphenyl) -3-methyl-1H-pyrazol-4-yl]pyridin-2-amine;
- 4- [5- (4-chlorophenyl) -3-methyl-1H-pyrazol-4-yl]pyridin-2-amine;
- 10 4- [5- (4-fluorophenyl) -3-methyl-1H-pyrazol-4-yl]pyridin-2-amine;
- 4- [5- (4-methoxyphenyl) -3-methyl-1H-pyrazol-4-yl]pyridin-2-amine;
- 15 5- [5- (3-chlorophenyl) -3-methyl-1H-pyrazol-4-yl] -2-methoxypyridine;
- 2-methoxy-5- [3-methyl-5- (3-methylphenyl) -1H-pyrazol-4-yl]pyridine;
- 2-methoxy-5- [5- (4-methoxyphenyl) -3-methyl-1H-pyrazol-4-yl]pyridine;
- 20 4- [5- (3-chlorophenyl) -3-methyl-1H-pyrazol-4-yl] -2-methoxypyridine;
- 2-methoxy-4- [3-methyl-5- (3-methylphenyl) -1H-pyrazol-4-yl]pyridine;
- 25 2-methoxy-4- [3-methyl-5- (2-methylphenyl) -1H-pyrazol-4-yl]pyridine;
- 4- [5- (4-chlorophenyl) -3-methyl-1H-pyrazol-4-yl] -2-methoxypyridine;
- 4- [5- (4-fluorophenyl) -3-methyl-1H-pyrazol-4-yl] -2-methoxypyridine;
- 30 2-methoxy-4- [3-methyl-5- (4-methylphenyl) -1H-pyrazol-4-yl]pyridine;
- 5- [5- (3-chlorophenyl) -3-methyl-1H-pyrazol-4-yl]pyridin-2-ol;
- 35 4- [5- (3-chlorophenyl) -3-methyl-1H-pyrazol-4-yl]pyridin-2-ol;

- 4- [5- (3-methylphenyl) -3-methyl-1H-pyrazol-4-yl]pyridin-2-  
ol;  
4- [5- (2-methylphenyl) -3-methyl-1H-pyrazol-4-yl]pyridin-2-  
ol;  
5 4- [5- (4-chlorophenyl) -3-methyl-1H-pyrazol-4-yl]pyridin-2-  
ol;  
4- [5- (4-fluorophenyl) -3-methyl-1H-pyrazol-4-yl]pyridin-2-  
ol;  
4- [5- (4-methoxyphenyl) -3-methyl-1H-pyrazol-4-yl]pyridin-  
10 2-ol;  
5- [5- (3-chlorophenyl) -3-methyl-1H-pyrazol-4-yl]pyridine-  
2-methanamine;  
4- [5- (3-chlorophenyl) -3-methyl-1H-pyrazol-4-yl]pyridine-  
2-methanamine;  
15 4- [5- (3-methylphenyl) -3-methyl-1H-pyrazol-4-yl]pyridine-  
2-methanamine;  
4- [5- (2-methylphenyl) -3-methyl-1H-pyrazol-4-yl]pyridine-  
2-methanamine;  
4- [5- (4-chlorophenyl) -3-methyl-1H-pyrazol-4-yl]pyridine-  
20 2-methanamine;  
4- [5- (4-fluorophenyl) -3-methyl-1H-pyrazol-4-yl]pyridine-  
2-methanamine;  
4- [5- (4-methoxyphenyl) -3-methyl-1H-pyrazol-4-yl]pyridine-  
2-methanamine;  
25 5- [5- (3-chlorophenyl) -3-methyl-1H-pyrazol-4-yl]pyridine-  
2-carboxamide;  
4- [5- (3-chlorophenyl) -3-methyl-1H-pyrazol-4-yl]pyridine-  
2-carboxamide;  
4- [5- (3-methylphenyl) -3-methyl-1H-pyrazol-4-yl]pyridine-  
30 2-carboxamide;  
4- [5- (2-methylphenyl) -3-methyl-1H-pyrazol-4-yl]pyridine-  
2-carboxamide;  
4- [5- (4-chlorophenyl) -3-methyl-1H-pyrazol-4-yl]pyridine-  
2-carboxamide;  
35 4- [5- (4-fluorophenyl) -3-methyl-1H-pyrazol-4-yl]pyridine-  
2-carboxamide;

- 4- [5- (4-methoxyphenyl) -3-methyl-1H-pyrazol-4-yl]pyridine-2-carboxamide;  
4- [5- (3-fluoro-4-methoxyphenyl) -3-methyl-1H-pyrazol-4-yl]pyridine;  
5 4- [5- (4-fluoro-3-methoxyphenyl) -3-methyl-1H-pyrazol-4-yl]pyridine;  
4- [5- (4-chloro-3-methoxyphenyl) -3-methyl-1H-pyrazol-4-yl]pyridine;  
4- [5- (2,3-dihydrobenzofuran-6-yl) -3-methyl-1H-pyrazol-4-yl]pyridine;  
10 4- [5- (benzofuran-6-yl) -3-methyl-1H-pyrazol-4-yl]pyridine;  
4- [5- (3-fluoro-5-methoxyphenyl) -3-methyl-1H-pyrazol-4-yl]pyridine;  
4- [5- (3-chloro-5-methoxyphenyl) -3-methyl-1H-pyrazol-4-yl]pyridine;  
15 4- [5- (1-cyclohexylen-1-yl) -3-methyl-1H-pyrazol-4-yl]pyridine;  
4- [5- (1,3-cyclohexadien-1-yl) -3-methyl-1H-pyrazol-4-yl]pyridine;  
20 4- [5- (5,6-dihydro-2H-pyran-4-yl) -3-methyl-1H-pyrazol-4-yl]pyridine;  
4- (5-cyclohexyl-3-methyl-1H-pyrazol-4-yl)pyridine;  
4- [5- (4-methoxy-3-methylphenyl) -3-methyl-1H-pyrazol-4-yl]pyridine;  
25 4- [5- (3-methoxy-4-methylphenyl) -3-methyl-1H-pyrazol-4-yl]pyridine;  
4- [5- (3-methoxy-5-methylphenyl) -3-methyl-1H-pyrazol-4-yl]pyridine;  
4- [5- (3-furyl) -3-methyl-1H-pyrazol-4-yl]pyridine;  
30 2-methyl-4- (3-methyl-5-phenyl-1H-pyrazol-4-yl)pyridine;  
2-methoxy-4- (3-methyl-5-phenyl-1H-pyrazol-4-yl)pyridine;  
methyl 4- (3-methyl-5-phenyl-1H-pyrazol-4-yl)pyridine-2-carboxylate;  
4- (3-methyl-5-phenyl-1H-pyrazol-4-yl)pyridine-2-carboxamide;  
35 1- [4- (3-methyl-5-phenyl-1H-pyrazol-4-yl)pyridin-2-

- yl]ethanone;  
N,N-dimethyl-4-(3-methyl-5-phenyl-1H-pyrazol-2-yl)pyridin-2-amine;  
3-methyl-4-(3-methyl-5-phenyl-1H-pyrazol-4-yl)pyridine;  
5 3-methoxy-4-(3-methyl-5-phenyl-1H-pyrazol-4-yl)pyridine;  
methyl 4-(3-methyl-5-phenyl-1H-pyrazol-4-yl)pyridine-3-carboxylate;  
4-(3-methyl-5-phenyl-1H-pyrazol-4-yl)pyridine-3-carboxamide;  
10 1-[4-(3-methyl-5-phenyl-1H-pyrazol-4-yl)pyridin-3-yl]ethanone;  
3-bromo-4-(3-methyl-5-phenyl-1H-pyrazol-4-yl)pyridine;  
N,N-dimethyl-4-(3-methyl-5-phenyl-1H-pyrazol-2-yl)pyridin-3-amine;  
15 2-methyl-4-(3-methyl-5-phenyl-1H-pyrazol-4-yl)pyrimidine;  
4-(3-methyl-5-phenyl-1H-pyrazol-4-yl)pyrimidine;  
2-methoxy-4-(3-methyl-5-phenyl-1H-pyrazol-4-yl)pyrimidine;  
4-(3-methyl-5-phenyl-1H-pyrazol-4-yl)pyrimidin-2-amine;  
20 N,N-dimethyl-4-(3-methyl-5-phenyl-1H-pyrazol-4-yl)pyrimidin-2-amine;  
4-(5,6-dihydro-2H-pyran-4-yl)-3-methyl-5-phenyl-1H-pyrazole;  
3-methyl-5-phenyl-4-(3-thienyl)-1H-pyrazole;  
25 4-(3-furyl)-3-methyl-5-phenyl-1H-pyrazole;  
3-methyl-5-phenyl-4-(2-thienyl)-1H-pyrazole;  
4-(2-furyl)-3-methyl-5-phenyl-1H-pyrazole;  
4-(3-isothiazolyl)-3-methyl-5-phenyl-1H-pyrazole;  
4-(3-isoxazolyl)-3-methyl-5-phenyl-1H-pyrazole;  
30 4-(5-isothiazolyl)-3-methyl-5-phenyl-1H-pyrazole;  
4-(5-isoxazolyl)-3-methyl-5-phenyl-1H-pyrazole;  
3-methyl-5-phenyl-4-(5-thiazolyl)-1H-pyrazole;  
3-methyl-4-(5-oxazolyl)-5-phenyl-1H-pyrazole;  
4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]pyridine;  
35 2-methyl-4-[3-(3-methylphenyl)-1H-pyrazol-4-yl]pyridine;  
4-(1-methyl-3-phenyl-1H-pyrazol-4-yl)pyridine;

- 4- (3-phenyl-1H-pyrazol-4-yl)pyridine;  
2-methyl-4- (3-phenyl-1H-pyrazol-4-yl)pyridine;  
4- [3- (3-chlorophenyl) -1-methyl-pyrazol-4-yl]pyridine;  
4- [3- (4-chlorophenyl) -1-methyl-pyrazol-4-yl]pyridine;  
5 4- [3- (3-chlorophenyl) -1H-pyrazol-4-yl]pyridine;  
4- [3- (4-chlorophenyl) -1H-pyrazol-4-yl]pyridine;  
4- [3- (3-chlorophenyl) -1H-pyrazol-4-yl] -2-methylpyridine;  
4- [3- (3-fluorophenyl) -1-methyl-1H-pyrazol-4-yl]pyridine;  
4- [3- (3-fluorophenyl) -1H-pyrazol-4-yl]pyridine;  
10 4- [3- (3-chlorophenyl) -1-methyl-pyrazol-4-yl] -2-  
methylpyridine;  
5- (4-chlorophenyl) -N-phenyl-4- (4-pyridinyl) -1H-pyrazol-3-  
amine;  
5- (4-chlorophenyl) -N-methyl-4- (4-pyridinyl) -1H-pyrazol-3-  
15 amine;  
5- (4-chlorophenyl) -N,N-dimethyl-4- (4-pyridinyl) -1H-  
pyrazol-3-amine dihydrate;  
5- (3-fluorophenyl) -N,N-dimethyl-4- (4-pyridinyl) -1H-  
pyrazol-3-amine;  
20 N,N-dimethyl-5- (3-methylphenyl) -4- (4-pyridinyl) -1H-  
pyrazol-3-amine;  
N-methyl-5- (3-methylphenyl) -4- (4-pyridinyl) -1H-pyrazol-3-  
amine;  
N-ethyl-5- (3-methylphenyl) -4- (4-pyridinyl) -1H-pyrazol-3-  
25 amine;  
N,N-diethyl-5- (3-methylphenyl) -4- (4-pyridinyl) -1H-  
pyrazol-3-amine;  
5- (4-chlorophenyl) - N,N-diethyl-4- (4-pyridinyl) -1H-  
pyrazol-3-amine;  
30 4- [5- (4-chlorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-  
yl]morpholine;  
5- (4-chlorophenyl) -N-propyl-4- (4-pyridinyl) -1H-pyrazol-3-  
amine;  
5- (4-chlorophenyl) -N- (phenylmethyl) -4- (4-pyridinyl) -1H-  
35 pyrazol-3-amine hydrate (2:1);  
5- (4-chlorophenyl) -N- (2-methoxyethyl) -4- (4-pyridinyl) -1H-

pyrazol-3-amine monohydrate;  
1,1-dimethylethyl 4-[5-(4-chlorophenyl)-4-(4-pyridinyl)-  
1H-pyrazol-3-yl]-1-piperazinecarboxylate;  
1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-  
5 yl]piperazine trihydrochloride;  
1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-  
methylpiperazine;  
1,1-dimethylethyl 4-[5-(4-fluorophenyl)-4-(4-pyridinyl)-  
1H-pyrazol-3-yl]-1-piperazinecarboxylate;  
10 1-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-  
yl]piperazine trihydrochloride;  
1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-  
yl]piperazine;  
N-[5-(4-chlorophenyl)-4-[2-(phenylmethyl)amino]-4-  
15 pyridinyl]-1H-pyrazol-3-yl]-1,3-propanediamine,  
trihydrochloride;  
1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-  
(phenylmethyl)piperazine;  
4-[3-(4-fluorophenyl)-5-(1-piperazinyl)-1H-pyrazol-4-  
20 yl]pyrimidine, dihydrochloride;  
1,1-dimethylethyl [3-[[5-(4-chlorophenyl)-4-(4-  
pyridinyl)-1H-pyrazol-3-yl]amino]propyl]carbamate;  
N-[5-[4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-  
1,3-propanediamine, trihydrochloride monohydrate;  
25 1,1-dimethylethyl [2-[[5-(4-chlorophenyl)-4-(4-  
pyridinyl)-1H-pyrazol-3-yl]amino]ethyl]carbamate;  
1,1-dimethylethyl 4-[5-(4-chlorophenyl)-1-(2-  
hydroxyethyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1-  
piperazinecarboxylate;  
30 1,1-dimethylethyl 4-[5-(4-fluorophenyl)-4-(4-  
pyrimidinyl)-1H-pyrazol-3-yl]-1-piperazinecarboxylate;  
1,1-dimethylethyl [3-[[5-(4-chlorophenyl)-4-(2-fluoro-4-  
pyridinyl)-1H-pyrazol-3-yl]amino]propyl]carbamate;  
1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-  
35 ethylpiperazine;  
N-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-



1,2-ethanediamine;  
4-[3-(2,6-difluorophenyl)-5-methyl-1H-pyrazol-4-yl]pyridine;  
4-[3-(3-ethylphenyl)-5-methyl-1H-pyrazol-4-yl]pyridine;  
5 4-[3-(3-chlorophenyl)-5-ethyl-1H-pyrazol-4-yl]pyridine;  
4-[3-ethyl-5-(3-ethylphenyl)-1H-pyrazol-4-yl]pyridine;  
4-[3-(4-chlorophenyl)-5-(1-methylethyl)-1H-pyrazol-4-yl]pyridine;  
4-[3-cyclopropyl-5-(4-fluorophenyl)-1H-pyrazol-4-yl]pyridine;  
10 4-[3-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-4-yl]pyridine;  
4-[5-(cyclopropyl-3-(4-(fluorophenyl)-1-methyl-1H-pyrazol-4-yl)]pyridine;  
15 5-cyclopropyl-3-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazole-1-ethanol;  
3-(4-fluorophenyl)-5-(2-methoxy-4-pyridinyl)-4-(4-pyridinyl)-1H-pyrazole-1-ethanol;  
4-[3-(4-fluorophenyl)-1-(2-hydroxyethyl)-4-(4-pyridinyl)-1H-pyrazol-5-yl]-2(1H)-pyridinone;  
20 1-acetyl-4-[3-(4-fluorophenyl)-1-(2-hydroxyethyl)-4-(4-pyridinyl)-1H-pyrazol-5-yl]-2(1H)-pyridinone;  
Ethyl 2-[3-(4-fluorophenyl)-1-(2-hydroxyethyl)-4-(4-pyridinyl)-1H-pyrazol-5-yl]cyclopropanecarboxylate;  
25 2-[3-(4-fluorophenyl)-1-(2-hydroxyethyl)-4-(4-pyridinyl)-1H-pyrazol-5-yl]cyclopropanecarboxylic acid;  
3-(4-fluorophenyl)-5-(4-imidazolyl)-4-(4-pyridinyl)-1H-pyrazole-1-ethanol;  
4-[3-(4-chloro-3-methylphenyl)-1H-pyrazol-4-yl]pyridine  
30 5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazole-3-carboxylic acid;  
5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazole-3-methanol;  
1-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]carbonyl]piperazine;  
35 1,1-dimethylethyl 4-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-

- 1H-pyrazol-3-yl]carbonyl]-1-piperazinecarboxylate;  
4-(1,5-dimethyl-3-phenyl-1H-pyrazol-4-yl)pyridine;  
4-(1,3-dimethyl-5-phenyl-1H-pyrazol-4-yl)pyridine;  
4-[3-(4-chlorophenyl)-1,5-dimethyl-1H-pyrazol-4-  
5 yl]pyridine;  
4-[5-(4-chlorophenyl)-1,3-dimethyl-1H-pyrazol-4-  
yl]pyridine;  
4-[5-ethyl-1-methyl-3-(3-methylphenyl)-1H-pyrazol-4-  
yl]pyridine;  
10 4-[3-ethyl-1-methyl-5-(3-methylphenyl)-1H-pyrazol-4-  
yl]pyridine;  
4-[3-(4-chlorophenyl)-1-ethyl-5-methyl-1H-pyrazol-4-  
yl]pyridine;  
4-[3-(4-chlorophenyl)-2-ethyl-5-methyl-1H-pyrazol-4-  
15 yl]pyridine;  
4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]pyridine;  
4-[3-(2-chlorophenyl)-1H-pyrazol-4-yl]pyridine;  
3-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazole-1-ethanol;  
3-(4-fluorophenyl)-4-(4-pyrimidinyl)-1H-pyrazole-1-  
20 ethanol;  
4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]pyridine;  
2-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-  
pyridinyl]amino]-1-butanol;  
4-[5-bromo-3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-  
25 yl]pyridine;  
4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-  
pyridinecarbonitrile;  
4-[2-[3-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-1-  
yl]ethyl]morpholine;  
30 3-(4-fluorophenyl)-1-methyl- $\alpha$ -phenyl-4-(4-pyridinyl)-1H-  
pyrazole-5-methanol;  
N-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-  
morpholineethanamine;  
4-[3-(3-chlorophenyl)-1H-pyrazol-4-yl]-2(1H)-pyridinone  
35 hydrazone;  
4-[3-(3-chlorophenyl)-1H-pyrazol-4-yl]-N-(phenylmethyl)-

- 2-pyridinamine;  
4-[3-(3-chlorophenyl)-1H-pyrazol-4-yl]-N-(phenylethyl)-2-pyridinamine;  
4-[3-(3-chlorophenyl)-1H-pyrazol-4-yl]-N-ethyl-2-pyridinamine;  
5 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinecarboxamide;  
Methyl 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinecarboxylate;  
10 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N-methyl-2-pyridinecarboxamide;  
4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinecarboxylic acid;  
4-[3-(3-fluorophenyl)-1H-pyrazol-4-yl]pyridine;  
15 4-[3-(1,3-benzodioxol-5-yl)-1H-pyrazol-4-yl]pyridine 4-[3-(3-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]pyridine;  
4-[3-(4-chlorophenyl)-1H-pyrazol-4-yl]pyridine;  
4-[3-(1,3-benzodioxol-5-yl)-1-methyl-1H-pyrazol-4-yl]pyridine;  
20 4-[3-(4-chlorophenyl)-1-methyl-1H-pyrazol-4-yl]pyridine;  
4-[3-(3-chlorophenyl)-1-methyl-1H-pyrazol-4-yl]-2-methylpyridine; 4-[5-(3-chlorophenyl)-1-methyl-1H-pyrazol-4-yl]-2-methylpyridine;  
4-[3-(3-chlorophenyl)-1-methyl-1H-pyrazol-4-yl]pyridine;  
25 4-[5-(3-chlorophenyl)-1-methyl-1H-pyrazol-4-yl]pyridine;  
2-methyl-4-[1-methyl-3-(3-methylphenyl)-1H-pyrazol-4-yl]pyridine;  
2-methyl-4-[1-methyl-5-(3-methylphenyl)-1H-pyrazol-4-yl]pyridine;  
30 4-(3-phenyl-1H-pyrazol-4-yl)pyridine;  
4-[3-[3-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl]pyridine;  
4-[1-methyl-3-[3-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl]pyridine;  
35 4-[3-(3,4-difluorophenyl)-1H-pyrazol-4-yl]pyridine;  
4-[3-(4-chlorophenyl)-1H-pyrazol-4-yl]-2-fluoropyridine;

- 4- [3- (4-bromophenyl) -1H-pyrazol-4-yl]pyridine;  
4- [3- (3,4-difluorophenyl) -1-methyl-1H-pyrazol-4-yl]pyridine;  
4- [3- (4-bromophenyl) -1-methyl-1H-pyrazol-4-yl]pyridine;  
5 (E) -4- [3- (4-fluorophenyl) -1H-pyrazol-4-yl] -2- (2-phenyleth  
enyl)pyridine;  
(S) -4- [3- (4-chlorophenyl) -1H-pyrazol-4-yl] -N- (2-methylbut  
yl) - 2-pyridinamine;  
4- [3- (4-chlorophenyl) -1H-pyrazol-4-yl] -N- [(4-methoxy-  
10 phenyl)methyl] - 2-pyridinamine;  
N- [4- [3- (4-chlorophenyl) -1H-pyrazol-4-yl] -2-pyridinyl] -  
2-pyridinemethanamine;  
N- [4- [3- (4-fluorophenyl) -1H-pyrazol-4-yl] -2-pyridinyl] -  
2-pyridinemethanamine;  
15 2-fluoro-4- [3- (4-fluorophenyl) -1H-pyrazol-4-yl]pyridine;  
4- [3- (4-iodophenyl) -1H-pyrazol-4-yl]pyridine;  
4- [3- (4-iodophenyl) -1-methyl-1H-pyrazol-4-yl]pyridine;  
4- [1-methyl-3- [4- (trifluoromethyl)phenyl] -1H-pyrazol-4-yl  
]pyridine;  
20 N- [1- (4-fluorophenyl)ethyl] -4- [3- (4-fluorophenyl) -1H-pyraz  
ol-4-yl] -2-pyridinamine;  
N- [(3-fluorophenyl)methyl] -4- [3- (4-fluorophenyl) -1H-pyraz  
ol-4-yl] -2-pyridinamine;  
4- [3- (4-fluorophenyl) -1-methyl-1H-pyrazol-4-yl] -2- (1-  
25 methylhydrazino)pyridine;  
2-fluoro-4- [3- (4-fluorophenyl) -1-methyl-1H-pyrazol-4-yl]p  
yridine;  
4- [3- (3,4-difluorophenyl) -1H-pyrazol-4-yl] -2-fluoro-  
pyridine;  
30 4- [3- (4-fluorophenyl) -1H-pyrazol-4-yl] -3-methylpyridine;  
4- [3- (4-fluorophenyl) -1-methyl-1H-pyrazol-4-yl] -3-methyl-  
pyridine;  
4- [3- (3,4-difluorophenyl) -1-methyl-1H-pyrazol-4-yl] -2-flu  
oropyridine;  
35 3- (4-fluorophenyl) -N,N-dimethyl-4- (4-pyridinyl) -1H-pyrazo  
le-1-ethanamine;

- 2- [2- (4-fluorophenyl) ethyl] -4- [3- (4-fluorophenyl) -1-methyl-1H-pyrazol-4-yl] pyridine;  
4- [3- (4-fluorophenyl) -1H-pyrazol-4-yl] -N- [1- (phenylmethyl) -4-piperidinyl] -2-pyridinamine;  
5 N' - [4- [3- (4-fluorophenyl) -1H-pyrazol-4-yl] -2-pyridinyl] -N,N-dimethyl-1,2-ethanediamine;  
2,4-bis [3- (4-fluorophenyl) -1H-pyrazol-4-yl] pyridine;  
N- [4- [3- (4-fluorophenyl) -1H-pyrazol-4-yl] -2-pyridinyl] -4-morpholineethanamine;  
10 3- (4-fluorophenyl) -4- (2-fluoro-4-pyridinyl) -1H-pyrazole-1-ethanol;  
4- [3- (4-fluorophenyl) -1H-pyrazol-4-yl] -N- [2- (1H-imidazol-1-yl) ethyl] -2-pyridinamine;  
4- [2- [3- (4-fluorophenyl) -4- (2-fluoro-4-pyridinyl) -1H-pyrazol-1-yl] ethyl] morpholine;  
15 (E) -3- (4-fluorophenyl) -4- [2- [2- (4-fluorophenyl) ethenyl] -4-pyridinyl] -1H-pyrazole-1-ethanol;  
3- (4-fluorophenyl) -4- (2-fluoro-4-pyridinyl) -N,N-dimethyl-1H-pyrazole-1-ethanamine;  
20 3- (4-fluorophenyl) -4- [2- [2- (4-fluorophenyl) ethyl] -4-pyridinyl] -1H-pyrazole-1-ethanol;  
4- [1- [2- (dimethylamino) ethyl] -3- (4-fluorophenyl) -1H-pyrazol-4-yl] -N,N-dimethyl-2-pyridinamine;  
4- [1- [2- (dimethylamino) ethyl] -3- (4-fluorophenyl) -1H-pyrazol-4-yl] -N- [(4-fluorophenyl) methyl] -2-pyridinamine;  
25 3- (4-fluorophenyl) -4- [2- [2- (4-fluorophenyl) ethyl] -4-pyridinyl] -N,N-dimethyl-1H-pyrazole-1-ethanamine;  
N- [(4-fluorophenyl) methyl] -4- [3 (or 5) - (4-fluorophenyl) -1- [2- (4-morpholinyl) ethyl] -1H-pyrazol-4-yl] -2-pyridinamine;  
30 4- [3- (4-fluorophenyl) -1H-pyrazol-4-yl] -N-4-piperadinyl-2-pyridinamine;  
N,N-diethyl-3- (4-fluorophenyl) -4- (2-fluoro-4-pyridinyl) -1H-pyrazole-1-ethanamine;  
35 4- [1- [2- (diethylamino) ethyl] -3- (4-fluorophenyl) -1H-pyrazol-4-yl] -N- [(4-fluorophenyl) methyl] -2-pyridinamine;

- 2-[[4-[3-(4-(fluorophenyl)-1H-pyrazol-4-yl)-2-pyridinyl]amino]ethanol;  
2-[[4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-2-pyridinyl]amino]ethanol;  
5 3-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]-1-propanol;  
3-(4-fluorophenyl)-4-[2-[[4-(4-fluorophenyl)methyl]amino]-4-pyridinyl]-1H-pyrazole-1-ethanol;  
5-(4-fluorophenyl)-4-[2-[[4-(4-fluorophenyl)methyl]amino]-4-pyridinyl]-1H-pyrazole-1-ethanol;  
10 N,N-diethyl-3-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazole-1-ethanamine;  
N-[(4-fluorophenyl)methyl]-4-[3-(4-fluorophenyl)-1-[2-(4-morpholinyl)ethyl]-1H-pyrazol-4-yl]-2-pyridinamine;  
15 N-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-morpholinepropanamine;  
N'-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-N,N-dimethyl-1,3-propanediamine;  
5-(4-fluorophenyl)-N-2-propynyl-4-(4-pyridinyl)-1H-pyrazol-3-amine;  
20 3-(4-fluorophenyl)-4-[2-[[4-(4-fluorophenyl)methyl]amino]-4-pyridinyl]-1H-pyrazole-1-ethanol;  
5-(4-fluorophenyl)-4-[2-[[4-(4-fluorophenyl)methyl]amino]-4-pyridinyl]-1H-pyrazole-1-ethanol;  
25 4-[3-[(4-fluorophenyl)-1H-pyrazol-4-yl]quinoline;  
N-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]glycine methyl ester;  
N-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]glycine;  
30 4-[3-(4-fluorophenyl)-1-(2-propynyl)-1H-pyrazol-4-yl]pyridine;  
4-[5-(4-fluorophenyl)-1-(2-propynyl)-1H-pyrazol-4-yl]pyridine;  
4,4'-(1H-pyrazole-3,4-diyl)bis[pyridine];  
35 4-[3-(3,4-dichlorophenyl)-1H-pyrazol-4-yl]pyridine;  
N-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-

piperidinamine;  
2-Chloro-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]pyrimidine;  
4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2(1H)-pyrimidinone  
5 hydrazone;  
4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N,N-dimethyl-2-pyrimidinamine;  
4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N-methyl-2-pyrimidinamine;  
10 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N-(phenylmethyl)-2-pyrimidinamine;  
N-cyclopropyl-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyrimidinamine;  
4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N-[(4-methoxyphenyl)methyl]-2-pyrimidinamine;  
15 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyrimidinamine;  
N-[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyrimidinyl]-N-(phenylmethyl)acetamide;  
Ethyl [4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyrimidinyl]carbamate;  
20 4-[3-(3-methylphenyl)-1H-pyrazol-4-yl]pyrimidine;  
4-[3-(4-chlorophenyl)-1H-pyrazol-4-yl]pyrimidine;  
4-[3-(3-fluorophenyl)-1H-pyrazol-4-yl]pyrimidine;  
4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]pyrimidine;  
25 1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-cyclopropylpiperazine;  
1-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-methylpiperazine, dihydrate;  
methyl 4-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1-piperazinecarboxylate,  
30 monohydrate;  
4-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-γ-oxo-1-piperazinebutanoic acid, dihydrate;  
4-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-γ-oxo-1-piperazinebutanoic acid, monosodium salt dihydrate;  
35 1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-

- (methylsulfonyl)piperazine, monohydrate;  
1- [5- (4-chlorophenyl) -4- (4-pyridinyl) -1- (2-propynyl) -1H-pyrazol-3-yl]piperazine, trihydrochloride monohydrate;  
4- [3- (4-fluorophenyl) -5- (1H-imidazol-4-yl) -1- (4-methoxyphenyl) -1H-pyrazol-4-yl]pyridine;  
5 4- [3- (4-fluorophenyl) -1H-pyrazol-4-yl] -N-2-propynyl-2-pyrimidinamine;  
N- (2-fluorophenyl) -4- [3- (4-fluorophenyl) -1H-pyrazol-4-yl] -2-pyrimidinamine;  
10 4- [3- (4-fluorophenyl) -1H-pyrazol-4-yl] -N- (2-methoxyphenyl) -2-pyrimidinamine;  
1- [5- (3-chlorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -4-methylpiperazine;  
N- [5- (4-fluorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -4-piperidinamine, trihydrochloride;  
15 N- [5- (4-fluorophenyl) -4- (pyridinyl) -1H-pyrazol-3-yl] -1-methyl-4-piperidinamine;  
ethyl 4- [[5- (4-fluorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] amino] -1-piperidinecarboxylate, monohydrate;  
20 1- [5- (4-chlorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -4- (2-methoxyphenyl) piperazine;  
1- [5- (4-chlorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -4-phenylpiperazine;  
N- [5- (4-chlorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -1-methyl-4-piperidinamine;  
25 1- [5- (4-chlorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -4- (2-propynyl) piperazine;  
1- [5- (4-chlorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] piperazine;  
30 1,1-dimethylethyl [3- [[5- (4-chlorophenyl) -4- (2- (phenylmethyl) amino] -4-pyridinyl-1H-pyrazol-3-yl] amino] propyl] carbamate;  
1,1-dimethylethyl 4- [5- (4-chlorophenyl) -4- (2-fluoro-4-pyridinyl) -1H-pyrazol-3-yl] -1-piperazinecarboxylate;  
35 ethyl 4- [[5- (4-chlorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] amino] -1-piperidinecarboxylate;



- 1- (4-chlorophenyl)-2- (1,3-dithietan-2-ylidene)-2- (4-pyridinyl) ethanone;
- 4- [3- (4-fluorophenyl)-5- [(1-methyl-4-piperidinyl)methyl]-1H-pyrazol-4-yl]pyridine;
- 5 1,1-dimethylethyl 4- [[5- (4-fluorophenyl)-4- (4-pyridinyl)-1H-pyrazol-3-yl]carbonyl]-1-piperazinecarboxylate;
- 1- [[5- (4-fluorophenyl)-4- (4-pyridinyl)-1H-pyrazol-3-yl]methyl]-4-methylpiperazine;
- 1- [[5- (4-fluorophenyl)-4- (4-pyridinyl)-1H-pyrazol-3-yl]methyl]-4-piperazine;
- 10 4- [3- (4-fluorophenyl)-5- (4-piperidinylmethyl)-1H-pyrazol-4-yl]pyridine;
- N- [5- (4-chlorophenyl)-4- (4-pyridinyl)-3H-pyrazol-3-yl]-4-piperidineamine, trihydrochloride, monohydrate;
- 15 N- [5- (4-chlorophenyl)-4- (4-pyridinyl)-1H-pyrazol-3-yl]-4-N,1-dimethyl-4-piperidineamine, dihydrate
- 1- [2- [5- (4-chlorophenyl)-4- (4-pyridinyl)-1H-pyrazol-3-yl]ethyl]piperazine;
- 1- [2- [5- (4-chlorophenyl)-4- (4-pyridinyl)-1H-pyrazol-3-yl]ethyl]-4-methylpiperazine;
- 20 1- [2- [5- (4-fluorophenyl)-4- (4-pyridinyl)-1H-pyrazol-3-yl]ethyl]piperazine;
- 1- [2- [5- (4-fluorophenyl)-4- (4-pyridinyl)-1H-pyrazol-3-yl]ethyl]-4-methylpiperazine;
- 25 1- [[5- (4-chlorophenyl)-4- (4-pyridinyl)-1H-pyrazol-3-yl]methyl]piperazine;
- 1- [[5- (4-chlorophenyl)-4- (4-pyridinyl)-1H-pyrazol-3-yl]methyl]-4-methylpiperazine;
- 4- [5- (4-chlorophenyl)-4- (4-pyridinyl)-1H-pyrazol-3-yl]-1-piperazineethanol;
- 30 4- [5- (4-chlorophenyl)-4- (4-pyridinyl)-1H-pyrazol-3-yl]-1-piperazineethanamine;
- 4- [5- [4-fluorophenyl)-4- (4-pyridinyl)-1H-pyrazol-3-yl]-1-piperazineethanol;
- 35 4- [5- (4-fluorophenyl)-4- (4-pyridinyl)-1H-pyrazol-3-yl]-1-piperazineethanamine;

- 1 - [5- (4-chlorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -  
3,5-dimethylpiperazine;  
4 - [5- (4-chlorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -  
1,2,6-trimethylpiperazine;  
5 1 - [5- (4-fluorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -  
3,5-dimethylpiperazine;  
4 - [5- (4-fluorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -  
1,2,6-trimethylpiperazine;  
1 - [5- (4-chlorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -3-  
10 methylpiperazine;  
4 - [5- (4-chlorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -  
1,2-dimethylpiperazine;  
1 - [5- (4-fluorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -3-  
methylpiperazine;  
15 4 - [5- (4-fluorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -  
1,2-dimethylpiperazine;  
5- (4-chlorophenyl) -4- (4-pyridinyl) -N-3-pyrrolidinyl-1H-  
pyrazol-3-amine;  
5- (4-chlorophenyl) -N- (1-methyl-3-pyrrolidinyl) -4- (4-  
20 pyridinyl) -1H-pyrazol-3-amine;  
5- (4-fluorophenyl) -4- (4-pyridinyl) -N-3-pyrrolidinyl-1H-  
pyrazol-3-amine;  
5- (4-fluorophenyl) -N- (1-methyl-3-pyrrolidinyl) -4- (4-  
pyridinyl) -1H-pyrazol-3-amine;  
25 1 - [5- (4-chlorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -3-  
pyrrolidinamine;  
1 - [5- (4-chlorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -  
N,N-dimethyl-3-pyrrolidinamine;  
1 - [5- (4-fluorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -3-  
30 pyrrolidinamine;  
1 - [5- (4-fluorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -  
N,N-dimethyl-3-pyrrolidinamine;  
5- (4-chlorophenyl) -N- [(1-ethyl-2-pyrrolidinyl)methyl] -4-  
(4-pyridinyl) -1H-pyrazol-3-amine;  
35 5- (4-fluorophenyl) -N- [(1-ethyl-2-pyrrolidinyl)methyl] -4-  
(4-pyridinyl) -1H-pyrazol-3-amine;

- N- [5- (4-chlorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -3-piperidinamine;
- N- [5- (4-chlorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -1-methyl-3-piperidinamine;
- 5 N- [5- (4-fluorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -3-piperidinamine;
- N- [5- (4-fluorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -1-methyl-3-piperidinamine;
- 4- [5- (4-chlorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -2-piperazinemethanol;
- 10 4- [5- (4-chlorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -2-piperazinemethanamine;
- 4- [5- (4-chlorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -1-methyl-2-piperazinemethanol;
- 15 4- [5- (4-chlorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -1-methyl-2-piperazinemethanamine;
- 4- [5- (4-fluorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -2-piperazinemethanol;
- 4- [5- (4-fluorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -2-piperazinemethanamine;
- 20 4- [5- (4-fluorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -1-methyl-2-piperazinemethanol;
- 4- [5- (4-fluorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -1-methyl-2-piperazinemethanamine;
- 25 4- [3- (4-chlorophenyl) -5- (4-methyl-1-piperazinyl) -1H-pyrazol-4-yl] -N-methyl-2-pyrimidinamine;
- 4- [3- (4-fluorophenyl) -5- (4-methyl-1-piperazinyl) -1H-pyrazol-4-yl] -N-methyl-2-pyrimidinamine;
- 1- [[5- (4-chlorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl]methyl] -4-piperidinol;
- 30 1- [[5- (4-fluorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl]methyl] -4-piperidinol;
- 4- [3- (4-chlorophenyl) -5- (4-methyl-1-piperazinyl) -1H-pyrazol-4-yl]pyrimidine;
- 35 4- [3- (4-fluorophenyl) -5- (4-methyl-1-piperazinyl) -1H-pyrazol-4-yl]pyrimidine;

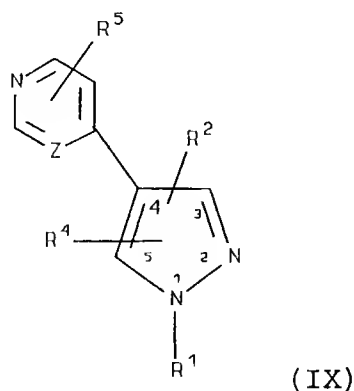
- 4- [5- (4-chlorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -2-  
piperazinecarboxylic acid;  
ethyl 4- [5- (4-chlorophenyl) -4- (4-pyridinyl) -1H-pyrazol-  
3-yl] -2-piperazinecarboxylate;
- 5 4- [5- (4-chlorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -1-  
methyl-2-piperazinecarboxylic acid;  
ethyl 4- [5- (4-chlorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-  
yl] -1-methyl-2-piperazinecarboxylate;
- 10 4- [5- (4-chlorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -1-  
methyl-2-piperazinecarboxamide;  
4- [5- (4-chlorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -2-  
piperazinecarboxamide;
- 15 4- [5- (4-fluorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -2-  
piperazinecarboxylic acid;  
ethyl 4- [5- (4-fluorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-  
yl] -2-piperazinecarboxylate;
- 20 4- [5- (4-fluorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -2-  
piperazinecarboxamide;  
4- [5- (4-fluorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -1-  
methyl-2-piperazinecarboxylic acid;
- 25 N- [5- (4-chlorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -1-  
ethyl-4-piperidinamine;  
N- [5- (4-chlorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -1-  
(phenylmethyl) -4-piperidinamine;
- 30 1-acetyl-N- [5- (4-chlorophenyl) -4- (4-pyridinyl) -1H-  
pyrazol-3-yl] -4-piperidinamine;  
N- [5- (4-chlorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -1-  
(2-propynyl) -4-piperidinamine;
- 35 N- [5- (4-chlorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -1-  
cyclopropyl-4-piperidinamine;  
N- [5- (4-chlorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -1-  
(methoxyacetyl) -4-piperidinamine;

- N-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1-(methylethyl)-4-piperidinamine;
- N-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1-propyl-4-piperidinamine;
- 5 ethyl 4-[[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]amino]-1-piperidinecarboxylate;
- 5-(4-fluorophenyl)-N-methyl-N-2-propynyl-4-(4-pyridinyl)-1H-pyrazol-3-amine;
- ( $\beta$ R)- $\beta$ -[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]benzene ethanol;
- 10 ( $\beta$ S)- $\beta$ -[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]benzene propanol;
- ( $\beta$ S)- $\beta$ -[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]benzene ethanol;
- 15 ( $\beta$ R)- $\beta$ -[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]benzene propanol;
- N-[2-(1-ethyl-2-piperidinyl)ethyl]-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinamine;
- N2,N2-diethyl-N1-[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]-1-phenyl-1,2-ethanediamine;
- 20 N-(1-ethyl-4-piperidinyl)-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinamine;
- 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N-(4-piperidinylmethyl)-2-pyridinamine;
- 25 2-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]-3-methyl-1-butanol;
- (2S)-2-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]-4-methyl-1-pentanol;
- N1,N1-diethyl-N4-[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyrimidinyl]-1,4-pentanediamine;
- 30 (2R)-1-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]-2-propanol;
- N4-[4-[3-(4-chlorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]-N1,N1-diethyl-1,4-pentanediamine;
- 35 (2S)-1-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]-2-propanol;

- 1- [5- (3,4-dichlorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -4-methylpiperazine;  
4- [3- (4-fluorophenyl) -1H-pyrazol-4-yl] -N- [2- (1-piperidinyl) ethyl] -2-pyridinamine;  
5 N,N-diethyl-N' - [4- [3- (4-fluorophenyl) -1H-pyrazol-4-yl] -2-pyridinyl] -1,2-ethanediamine;  
4- [3- (4-fluorophenyl) -1- (2-propenyl) -1H-pyrazol-4-yl] pyridine, monohydrochloride;  
8- [5- (4-fluorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -  
10 1,4-dioxo-8-azaspiro [4.5] decane;  
1- [5- (4-fluorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -4-piperidinone;  
1- [5- (4-fluorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -4-piperidinol;  
15 1- [5- (4-fluorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -1,2,3,6-hexahydropyridine;  
1- [5- (4-fluorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -N,N-dimethyl-4-piperidinamine, trihydrochloride;  
1- [5- (4-fluorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -4-  
20 piperidinamine, trihydrochloride;  
4- [3- (4-fluorophenyl) -5- (4- (1-pyrrolidinyl) -1-piperidinyl) -1H-pyrazol-4-yl] pyridine, trihydrochloride;  
ethyl 4- [[4- [3- (4-fluorophenyl) -1H-pyrazol-4-yl] -2-pyridinyl] amino] -1-piperidinecarboxylate;  
25 1-methyl-4- [5-phenyl-4- (4-pyridinyl) -1H-pyrazol-3-yl] piperazine;  
1- [5- (3,4-difluorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] -4-methylpiperazine;  
4- [5- (4-fluorophenyl) -4- (4-pyridinyl) -1H-pyrazol-3-yl] morpholine;  
30 N1,N1-diethyl-N4- [4- [3- (4-fluorophenyl) -1H-pyrazol-4-yl] -2-pyridinyl] -1,4-pentanediamine;  
4- [3- (4-fluorophenyl) -1H-pyrazol-4-yl] -N- [3- (2-methyl-1-piperidinyl) propyl] -2-pyridinamine;  
35 ethyl 4- [5-phenyl-4- (4-pyridinyl) -1H-pyrazol-3-yl] -1-piperazinecarboxylate;

- N,N-diethyl-N'-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1,3-propanediamine;  
 N1,N1,-diethyl-N4-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1,4-pentanediamine;  
 5 N-[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]-4-methyl-1-piperazinepropanamine (2E)-2-butenedioate (1:1);  
 N-(2-[1,4'-bipiperidin]-1'-ylethyl)-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinamine;  
 N-[2-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]ethyl]-N,N',N'-trimethyl-1,3-propanediamine;  
 10 N,N,N''-triethyl-N'-[2-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]ethyl]-1,3-propanediamine;  
 15 3-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]-1,2-propanediol;  
 trans-4-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]cyclohexanol;  
 4-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]cyclohexanone; and  
 20 1-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-N,N-diethyl-4-piperidinamine, trihydrochloride.

- Within Formula I there is another subclass of  
 25 compounds of high interest represented by Formula IX:



wherein

Z represents a carbon atom or a nitrogen atom; and

R<sup>1</sup> is selected from hydrido, lower alkyl, lower hydroxyalkyl, lower alkynyl, lower heterocycl, lower aralkyl, lower aminoalkyl and lower alkylaminoalkyl; and

R<sup>2</sup> is selected from hydrido, lower alkyl, aryl selected from phenyl, biphenyl, and naphthyl, 5- or 6-membered heterocyclyl selected from piperidinyl, piperazinyl, imidazolyl, pyridinyl and morpholinyl, lower haloalkyl, lower hydroxyalkyl, lower alkoxycarbonyl, lower alkylamino, lower alkylaminoalkyl, phenylamino, lower aralkyl, lower aralkylamino, lower alkylaminoalkylamino, lower aminoalkyl, lower aminoalkylamino, lower alkynylamino, lower heterocyclylamino, lower heterocyclylalkyl, lower heterocyclylalkylamino, lower alkylheterocyclyl, lower carboxycycloalkyl, lower carboxyalkylamino, lower alkoxyalkylamino, lower alkoxycarbonylaminoalkylamino, lower heterocyclylcarbonyl, lower alkoxycarbonylheterocyclyl, and lower alkoxycarbonylheterocyclylcarbonyl; wherein the aryl and heteroaryl groups are optionally substituted with one or more radicals independently selected from halo, lower alkyl, keto, aralkyl, carboxy, lower alkylaminoalkylamino, lower alkynylamino, lower heterocyclylalkylamino, lower alkylcarbonyl and lower alkoxycarbonyl; or

R<sup>2</sup> is -CR<sup>54</sup>R<sup>55</sup> wherein R<sup>54</sup> is phenyl and R<sup>55</sup> is hydroxy; and

R<sup>4</sup> is selected from hydrido, lower cycloalkyl, lower cycloalkenyl, lower cycloalkyldienyl, 5- or 6-membered heterocyclyl, and aryl selected from phenyl, biphenyl, naphthyl; wherein R<sup>4</sup> is optionally substituted at a substitutable position with one or more radicals independently selected from halo, lower alkyl, lower alkoxy, aryloxy, lower aralkoxy, lower haloalkyl, lower



alkylthio, lower alkylamino, nitro, hydroxy; and

R<sup>5</sup> is selected from halo, amino, cyano, aminocarbonyl, lower alkyl, lower alkoxy, hydroxy, lower aminoalkyl, lower aralkyl, lower aralkyloxy, lower  
5 aralkylamino, lower alkoxycarbonyl, lower alkylamino, lower alkylcarbonyl, lower aralkenyl, lower arylheterocyclyl, carboxy, lower cycloalkylamino, lower alkoxycarbonylamino, lower alkoxyaralkylamino, lower alkylaminoalkylamino, lower heterocyclylamino, lower  
10 heterocyclylalkylamino, lower aralkylheterocyclylamino, lower alkylaminocarbonyl, lower alkylcarbonyl, lower alkoxyaralkylamino, hydrazinyl, and lower alkylhydrazinyl, or -NR<sup>62</sup>R<sup>63</sup> wherein R<sup>62</sup> is lower alkylcarbonyl or amino, and R<sup>63</sup> is lower alkyl or lower  
15 phenylalkyl; or  
a pharmaceutically-acceptable salt or tautomer thereof.

A preferred class of compounds consists of those  
20 compounds of Formula IX

R<sup>1</sup> is selected from hydrido, methyl, ethyl, hydroxyethyl and propargyl; and

R<sup>2</sup> is selected from hydrido, methyl, ethyl, propyl, phenyl, trifluoromethyl, hydroxyethyl,  
25 methoxycarbonyl, ethoxycarbonyl, N-methylamino, N,N-dimethylamino, N-ethylamino, N,N-diethylamino, N-propylamino, N-phenylamino, aminomethyl, aminoethyl, aminoethylamino, aminopropylamino, propargylamino, benzylamino, dimethylaminopropylamino,  
30 morpholinylpropylamino, morpholinylethylamino, piperidinyl, piperazinyl, imidazolyl, morpholinyl, pyridinyl, carboxymethylamino, methoxyethylamino, (1,1-dimethyl)ethylcarbonyl, (1,1-dimethyl)ethylcarbonylamino, (1,1-dimethyl)ethylcarbonylaminoethylamino,  
35 piperazinylcarbonyl, 1,1-dimethyl-

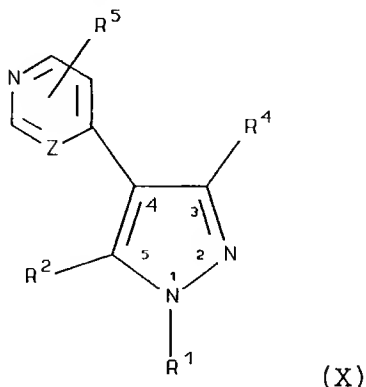
ethylpiperazinylcarbonyl; wherein the phenyl, piperidinyl, piperazinyl, imidazolyl, morpholinyl, and pyridinyl groups are optionally substituted with one or more radicals independently selected from fluoro, chloro, bromo, keto, methyl, ethyl, trifluoromethyl, benzyl, methoxy, methoxycarbonyl, ethoxycarbonyl and (1,1-dimethyl)ethoxycarbonyl; and

R<sup>4</sup> is selected from cyclohexyl, cyclohexenyl, cyclohexadienyl, phenyl, quinolyl, biphenyl, pyridinyl, thienyl, furyl, dihydropyranyl, benzofuryl, dihydrobenzofuryl, and benzodioxolyl; wherein R<sup>4</sup> is optionally substituted with one or more radicals independently selected from methylthio, fluoro, chloro, bromo, methyl, ethyl, methoxy, ethoxy, phenoxy, benzyloxy, trifluoromethyl, nitro, dimethylamino, and hydroxy; and

R<sup>5</sup> is selected from fluoro, chloro, bromo, methyl, fluorophenylethyl, fluorophenylethenyl, fluorophenylpyrazolyl, cyano, methoxycarbonyl, aminocarbonyl, acetyl, hydroxy, carboxy, methoxy, methylamino, dimethylamino, 2-methylbutylamino, ethylamino, dimethylaminoethylamino, hydroxypropylamino, hydroxyethylamino, imidazolylamino, morpholinylethylamino, (1-ethyl-2-hydroxy)ethylamino, piperidinylamino, pyridinylmethylamino, phenylmethylpiperidinylamino, aminomethyl, cyclopropylamino, amino, hydroxy, methylcarbonyl, ethoxycarbonylamino, methoxyphenylmethylamino, phenylmethylamino, fluorophenylmethylamino, fluorophenylethylamino, methylaminocarbonyl, methylcarbonyl, hydrazinyl, and 1-methylhydrazinyl, or -NR<sup>62</sup>R<sup>63</sup> wherein R<sup>62</sup> is methylcarbonyl or amino, and R<sup>63</sup> is methyl or benzyl; or

a pharmaceutically-acceptable salt or tautomer thereof.

Within Formula I there is another subclass of compounds of high interest represented by Formula X:



wherein

5        Z represents a carbon atom or a nitrogen atom; and  
       R<sup>1</sup> is selected from lower alkyl, lower hydroxyalkyl, lower alkynyl, lower aminoalkyl and lower alkylaminoalkyl; and

      R<sup>2</sup> is selected from hydrido, lower alkyl, aryl  
 10    selected from phenyl, biphenyl, and naphthyl, 5- or 6-membered heterocyclyl selected from piperidinyl, piperazinyl, imidazolyl, pyridinyl and morpholinyl, lower haloalkyl, lower hydroxyalkyl, lower alkoxy carbonyl, lower alkylamino, lower alkylaminoalkyl, phenylamino,  
 15    lower aralkyl, lower aralkylamino, lower alkylaminoalkylamino, lower aminoalkyl, lower aminoalkylamino, lower alkynylamino, lower heterocyclylamino, lower heterocyclylalkyl, lower heterocyclylalkylamino, lower alkylheterocyclyl, lower  
 20    carboxycycloalkyl, lower carboxyalkylamino, lower alkoxyalkylamino, lower alkoxy carbonylaminoalkylamino, lower heterocyclylcarbonyl, lower alkoxy carbonyl heterocyclyl, and lower alkoxy carbonyl heterocyclylcarbonyl; wherein the aryl and  
 25    heteroaryl groups are optionally substituted with one or

more radicals independently selected from halo, lower alkyl, keto, aralkyl, carboxy, lower alkylaminoalkylamino, lower alkynylamino, lower heterocyclalkylamino, lower alkylcarbonyl and lower alkoxy carbonyl; or

$R^2$  is  $-CR^{54}R^{55}$  wherein  $R^{54}$  is phenyl and  $R^{55}$  is hydroxy; and

$R^4$  is selected from 5- or 6-membered heteroaryl, and aryl selected from phenyl, biphenyl, and naphthyl;

wherein  $R^4$  is optionally substituted with one or more radicals independently selected from halo, lower alkyl, lower alkoxy, aryloxy, lower aralkoxy, lower haloalkyl, lower alkylthio, lower alkylamino, nitro, hydroxy; and

$R^5$  is selected from halo, amino, cyano, aminocarbonyl, lower alkyl, lower alkoxy, hydroxy, lower aminoalkyl, lower aralkyl, lower aralkyloxy, lower aralkylamino, lower alkoxy carbonyl, lower alkylamino, lower alkylcarbonyl, lower aralkenyl, lower arylheterocycl, carboxy, lower cycloalkylamino, lower alkoxy carbonylamino, lower alkoxyaralkylamino, lower alkylaminoalkylamino, lower heterocycllamino, lower heterocyclalkylamino, lower aralkylheterocycllamino, lower alkylaminocarbonyl, lower alkylcarbonyl, lower alkoxyaralkylamino, hydrazinyl, and lower alkylhydrazinyl, or  $-NR^{62}R^{63}$  wherein  $R^{62}$  is lower alkylcarbonyl or amino, and  $R^{63}$  is lower alkyl or lower phenylalkyl; or

a pharmaceutically-acceptable salt or tautomer thereof.

A preferred class of compounds consists of those compounds of Formula X

$R^1$  is selected from methyl, ethyl, hydroxyethyl and propargyl; and

$R^2$  is selected from methyl, ethyl, propyl, phenyl, trifluoromethyl, hydroxyethyl, methoxycarbonyl ethyl,

ethoxycarbonyl ethyl, N-methylamino, N,N-dimethylamino, N-ethylamino, N,N-diethylamino, N-propylamino, N-phenylamino, aminomethyl, aminoethyl, aminoethylamino, aminopropylamino, propargylamino, benzylamino, 5 piperadinylamino, dimethylaminoethylamino, dimethylaminopropylamino, morpholinylpropylamino, morpholinylethylamino, piperidinyl, piperazinyl, imidazolyl, morpholinyl, pyridinyl, N-methylpiperazinyl, carboxymethylamino, methoxyethylamino, (1,1- 10 dimethyl)ethylcarbonyl, (1,1-dimethyl)ethylcarbonylamino, (1,1-dimethyl)ethylcarbonylaminoethylamino, piperazinylcarbonyl, and 1,1-dimethyl-ethylpiperazinylcarbonyl; wherein the phenyl, 15 piperidinyl, piperazinyl, imidazolyl, morpholinyl, and pyridinyl groups are optionally substituted with one or more radicals independently selected from fluoro, chloro, bromo, keto, methyl, ethyl, trifluoromethyl, benzyl, methoxy, methoxycarbonyl, ethoxycarbonyl and (1,1- 20 dimethyl)ethoxycarbonyl; and

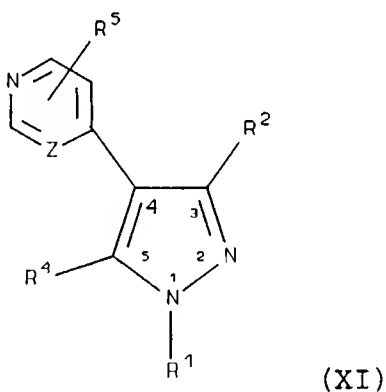
R<sup>4</sup> is selected from phenyl, quinolyl, biphenyl, pyridinyl, thienyl, furyl, dihydropyranyl, benzofuryl, dihydrobenzofuryl, and benzodioxolyl; wherein R<sup>4</sup> is optionally substituted with one or more radicals 25 independently selected from methylthio, fluoro, chloro, bromo, methyl, ethyl, methoxy, ethoxy, phenoxy, benzyloxy, trifluoromethyl, nitro, dimethylamino, and hydroxy; and

R<sup>5</sup> is selected from fluoro, chloro, bromo, methyl, 30 fluorophenylethyl, fluorophenylethenyl, fluorophenylpyrazolyl, cyano, methoxycarbonyl, aminocarbonyl, acetyl, hydroxy, carboxy, methoxy, methylamino, dimethylamino, 2-methylbutylamino, ethylamino, dimethylaminoethylamino, hydroxypropylamino, 35 hydroxyethylamino, propargylamino, imidazolylamino, morpholinylethylamino, (1-ethyl-2-hydroxy)ethylamino,

piperidinylamino, pyridinylmethylamino,  
 phenylmethylpiperidinylamino, aminomethyl,  
 cyclopropylamino, amino, hydroxy, methylcarbonyl,  
 ethoxycarbonylamino, methoxyphenylmethylamino,  
 5 phenylmethylamino, fluorophenylmethylamino,  
 fluorophenylethylamino, methylaminocarbonyl,  
 methylcarbonyl, hydrazinyl, and 1-methylhydrazinyl, or -  
 $\text{NR}^{62}\text{R}^{63}$  wherein  $\text{R}^{62}$  is methylcarbonyl or amino, and  $\text{R}^{63}$  is  
 methyl or benzyl; or

10 a pharmaceutically-acceptable salt or tautomer  
 thereof.

Within Formula I there is another subclass of  
 compounds of high interest represented by Formula XI:



wherein

Z represents a carbon atom or a nitrogen atom; and

$\text{R}^1$  is selected from lower alkyl, lower hydroxyalkyl,  
 lower alkynyl, lower aminoalkyl and lower  
 20 alkylaminoalkyl; and

$\text{R}^2$  is selected from hydrido, lower alkyl, aryl  
 selected from phenyl, biphenyl, and naphthyl, 5- or 6-  
 membered heterocyclyl selected from piperidinyl,  
 piperazinyl, imidazolyl, pyridinyl and morpholinyl, lower  
 25 haloalkyl, lower hydroxyalkyl, lower alkoxycarbonyl,

lower alkylamino, lower alkylaminoalkyl, phenylamino,  
lower aralkyl, lower aralkylamino, lower  
alkylaminoalkylamino, lower aminoalkyl, lower  
aminoalkylamino, lower alkynylamino, lower  
5 heterocyclylamino, lower heterocyclylalkyl, lower  
heterocyclylalkylamino, lower alkylheterocyclyl, lower  
carboxycycloalkyl, lower carboxyalkylamino, lower  
alkoxyalkylamino, lower alkoxycarbonylaminoalkylamino,  
lower heterocyclylcarbonyl, lower  
10 alkoxycarbonylheterocyclyl, and lower  
alkoxycarbonylheterocyclylcarbonyl; wherein the aryl and  
heteroaryl groups are optionally substituted with one or  
more radicals independently selected from halo, lower  
alkyl, keto, aralkyl, carboxy, lower  
15 alkylaminoalkylamino, lower alkynylamino, lower  
heterocyclylalkylamino, lower alkylcarbonyl and lower  
alkoxycarbonyl; or  
R<sup>2</sup> is -CR<sup>54</sup>R<sup>55</sup> wherein R<sup>54</sup> is phenyl and R<sup>55</sup> is hydroxy;  
and  
20 R<sup>4</sup> is selected from 5- or 6-membered heteroaryl, and  
aryl selected from phenyl, biphenyl, and naphthyl;  
wherein R<sup>4</sup> is optionally substituted with one or more  
radicals independently selected from halo, lower alkyl,  
lower alkoxy, aryloxy, lower aralkoxy, lower haloalkyl,  
25 lower alkylthio, lower alkylamino, nitro, hydroxy; and  
R<sup>5</sup> is selected from halo, amino, cyano,  
aminocarbonyl, lower alkyl, lower alkoxy, hydroxy, lower  
aminoalkyl, lower aralkyl, lower aralkyloxy, lower  
aralkylamino, lower alkoxycarbonyl, lower alkylamino,  
30 lower alkylcarbonyl, lower aralkenyl, lower  
arylheterocyclyl, carboxy, lower cycloalkylamino, lower  
alkoxycarbonylamino, lower alkoxyaralkylamino, lower  
alkylaminoalkylamino, lower heterocyclylamino, lower  
heterocyclylalkylamino, lower aralkylheterocyclylamino,  
35 lower alkylaminocarbonyl, lower alkylcarbonyl, lower  
alkoxyaralkylamino, hydrazinyl, and lower

alkylhydrazinyl, or  $-NR^{62}R^{63}$  wherein  $R^{62}$  is lower alkylcarbonyl or amino, and  $R^{63}$  is lower alkyl or lower phenylalkyl; or

5 a pharmaceutically-acceptable salt or tautomer thereof.

A preferred class of compounds consists of those compounds of Formula XI

10  $R^1$  is selected from methyl, ethyl, hydroxyethyl and propargyl; and

$R^2$  is selected from methyl, ethyl, propyl, phenyl, trifluoromethyl, hydroxyethyl, methoxycarbonyl ethyl, ethoxycarbonyl ethyl, N-methylamino, N,N-dimethylamino, N-ethylamino, N,N-diethylamino, N-propylamino, N-phenylamino, aminomethyl, aminoethyl, aminoethylamino, aminopropylamino, propargylamino, benzylamino, dimethylaminopropylamino, morpholinylpropylamino, morpholinylethylamino, piperidinyl, piperazinyl, imidazolyl, morpholinyl, pyridinyl, carboxymethylamino, methoxyethylamino, (1,1-dimethyl)ethylcarbonyl, (1,1-dimethyl)ethylcarbonylamino propylamino, (1,1-dimethyl)ethylcarbonylamino ethylamino, piperazinylcarbonyl, 1,1-dimethyl-ethylpiperazinylcarbonyl; wherein the phenyl, piperidinyl, piperazinyl, imidazolyl, morpholinyl, and pyridinyl groups are optionally substituted with one or more radicals independently selected from fluoro, chloro, bromo, keto, methyl, ethyl, trifluoromethyl, benzyl, methoxy, methoxycarbonyl, ethoxycarbonyl and (1,1-dimethyl)ethoxycarbonyl;

30  $R^4$  is selected from phenyl, quinolyl, biphenyl, pyridinyl, thienyl, furyl, dihydropyranyl, benzofuryl, dihydrobenzofuryl, and benzodioxolyl; wherein  $R^4$  is optionally substituted with one or more radicals independently selected from methylthio, fluoro, chloro, bromo, methyl, ethyl, methoxy, ethoxy, phenoxy,



benzyloxy, trifluoromethyl, nitro, dimethylamino, and hydroxy; and

R<sup>5</sup> is selected from fluoro, chloro, bromo, methyl, fluorophenylethyl, fluorophenylethenyl, fluorophenylpyrazolyl, cyano, methoxycarbonyl, aminocarbonyl, acetyl, hydroxy, carboxy, methoxy, methylamino, dimethylamino, 2-methylbutylamino, ethylamino, dimethylaminoethylamino, hydroxypropylamino, hydroxyethylamino, imidazolylamino, morpholinylethylamino, (1-ethyl-2-hydroxy)ethylamino, piperidinylamino, pyridinylmethylamino, phenylmethylpiperidinylamino, aminomethyl, cyclopropylamino, amino, hydroxy, methylcarbonyl, ethoxycarbonylamino, methoxyphenylmethylamino, phenylmethylamino, fluorophenylmethylamino, fluorophenylethylamino, methylaminocarbonyl, methylcarbonyl, hydrazinyl, and 1-methylhydrazinyl, or -NR<sup>62</sup>R<sup>63</sup> wherein R<sup>62</sup> is methylcarbonyl or amino, and R<sup>63</sup> is methyl or benzyl; or

a pharmaceutically-acceptable salt or tautomer thereof.

A preferred class of compounds consists of those compounds of Formula IX wherein

Z represents a carbon atom or a nitrogen atom; and R<sup>1</sup> is selected from hydrido, lower alkyl, lower hydroxyalkyl, lower alkynyl, lower aminoalkyl and lower alkylaminoalkyl; and

R<sup>2</sup> is selected from hydrido, lower alkyl, aryl selected from phenyl, biphenyl, and naphthyl, 5- or 6-membered heterocyclyl selected from piperidinyl, piperazinyl, imidazolyl, pyridinyl and morpholinyl, lower haloalkyl, lower hydroxyalkyl, lower alkoxycarbonyl, lower alkylamino, lower alkylaminoalkyl, phenylamino, lower aralkyl, lower aralkylamino, lower alkylaminoalkylamino, lower aminoalkyl, lower

aminoalkylamino, lower alkynylamino, lower  
heterocyclylamino, lower heterocyclylalkyl, lower  
heterocyclylalkylamino, lower alkylheterocyclyl, lower  
carboxycycloalkyl, lower carboxyalkylamino, lower  
5 alkoxyalkylamino, lower alkoxycarbonylaminoalkylamino,  
lower heterocyclylcarbonyl, lower  
alkoxycarbonylheterocyclyl, and lower  
alkoxycarbonylheterocyclylcarbonyl; wherein the aryl and  
heteroaryl groups are optionally substituted with one or  
10 more radicals independently selected from halo, lower  
alkyl, keto, aralkyl, carboxy, lower  
alkylaminoalkylamino, lower alkynylamino, lower  
heterocyclylalkylamino, lower alkylcarbonyl and lower  
alkoxycarbonyl; or

15  $R^2$  is  $-CR^{54}R^{55}$  wherein  $R^{54}$  is phenyl and  $R^{55}$  is hydroxy;  
and

$R^4$  is phenyl that is optionally substituted with one  
or more radicals independently selected from halo, lower  
alkyl, lower alkoxy, aryloxy, lower aralkoxy, lower  
20 haloalkyl, lower alkylthio, lower alkylamino, nitro,  
hydroxy; and

$R^5$  is selected from halo, amino, cyano,  
aminocarbonyl, lower alkyl, lower alkoxy, hydroxy, lower  
aminoalkyl, lower aralkyl, lower aralkyloxy, lower  
25 aralkylamino, lower alkoxycarbonyl, lower alkylamino,  
lower alkylcarbonyl, lower aralkenyl, lower  
arylheterocyclyl, carboxy, lower cycloalkylamino, lower  
alkoxycarbonylamino, lower alkoxyaralkylamino, lower  
alkylaminoalkylamino, lower heterocyclylamino, lower  
30 heterocyclylalkylamino, lower aralkylheterocyclylamino,  
lower alkylaminocarbonyl, lower alkylcarbonyl, lower  
alkoxyaralkylamino, hydrazinyl, and lower  
alkylhydrazinyl, or  $-NR^{62}R^{63}$  wherein  $R^{62}$  is lower  
alkylcarbonyl or amino, and  $R^{63}$  is lower alkyl or lower  
35 phenylalkyl; or

a pharmaceutically-acceptable salt or tautomer

thereof.

A class of compounds of specific interest consists of those compounds of Formula IX wherein

5         $R^1$  is selected from hydrido, methyl, ethyl, hydroxyethyl and propargyl;

$R^2$  is selected from methyl, ethyl, propyl, phenyl, trifluoromethyl, hydroxyethyl, methoxycarbonyl, ethoxycarbonyl, N-methylamino, N,N-dimethylamino, N-ethylamino, N,N-diethylamino, N-propylamino, N-phenylamino, aminomethyl, aminoethyl, aminoethylamino, aminopropylamino, propargylamino, benzylamino, dimethylaminopropylamino, morpholinylpropylamino, morpholinylethylamino, piperidinyl, piperazinyl, 10 imidazolyl, morpholinyl, pyridinyl, carboxymethylamino, methoxyethylamino, (1,1-dimethyl)ethylcarbonyl, (1,1-dimethyl)ethylcarbonylamino, (1,1-dimethyl)ethylcarbonylaminoethylamino, piperazinylcarbonyl, 1,1-dimethyl-ethylpiperazinylcarbonyl; wherein the phenyl, piperidinyl, piperazinyl, imidazolyl, morpholinyl, and pyridinyl groups are optionally substituted with one or more radicals independently selected from fluoro, chloro, bromo, keto, methyl, ethyl, trifluoromethyl, benzyl, methoxy, methoxycarbonyl, ethoxycarbonyl and (1,1-dimethyl)ethoxycarbonyl;

$R^4$  is phenyl that is optionally substituted with one or more radicals independently selected from methylthio, fluoro, chloro, bromo, methyl, ethyl, methoxy, ethoxy, phenoxy, benzyloxy, trifluoromethyl, nitro, dimethylamino, and hydroxy; and

$R^5$  is selected from fluoro, chloro, bromo, methyl, fluorophenylethyl, fluorophenylethenyl, fluorophenylpyrazolyl, cyano, methoxycarbonyl, aminocarbonyl, acetyl, hydroxy, carboxy, methoxy, methylamino, dimethylamino, 2-methylbutylamino,

ethylamino, dimethylaminoethylamino, hydroxypropylamino,  
hydroxyethylamino, imidazolylamino,  
morpholinylethylamino, (1-ethyl-2-hydroxy)ethylamino,  
piperidinylamino, pyridinylmethylamino,  
5 phenylmethylpiperidinylamino, aminomethyl,  
cyclopropylamino, amino, hydroxy, methylcarbonyl,  
ethoxycarbonylamino, methoxyphenylmethylamino,  
phenylmethylamino, fluorophenylmethylamino,  
fluorophenylethylamino, methylaminocarbonyl,  
10 methylcarbonyl, hydrazinyl, and 1-methylhydrazinyl, or -  
 $\text{NR}^{62}\text{R}^{63}$  wherein  $\text{R}^{62}$  is methylcarbonyl or amino, and  $\text{R}^{63}$  is  
methyl or benzyl; or

a pharmaceutically-acceptable salt or tautomer  
thereof.

15

Another class of compounds of specific interest  
consists of those compounds of Formula IX wherein

Z represents a carbon atom or a nitrogen atom;  
and

20

$\text{R}^1$  is selected from hydrido, lower alkyl, lower  
hydroxyalkyl and lower alkynyl; and

$\text{R}^2$  is selected from hydrido and lower alkyl; and

$\text{R}^4$  is selected from phenyl and benzodioxolyl; wherein  
phenyl is optionally substituted with one or more halo  
25 radicals; and

25

$\text{R}^5$  is selected from hydrido, halo and  
alkylhydrazinyl; or

a pharmaceutically-acceptable salt or tautomer  
thereof.

30

Still another class of compounds of specific  
interest consists of those compounds of Formula IX  
wherein;

Z represents a carbon atom; and

35

$\text{R}^1$  is selected from hydrido, methyl, hydroxyethyl,  
propargyl; and

R<sup>2</sup> is hydrido; and

R<sup>4</sup> is selected from phenyl and benzodioxolyl; wherein phenyl is optionally substituted with one or more radicals independently selected from chloro, fluoro and bromo; and

R<sup>5</sup> is selected from hydrido, fluoro, and 1-methylhydrazinyl; or

a pharmaceutically-acceptable salt or tautomer thereof.

A preferred class of compounds of specific interest consists of those compounds of Formula IX wherein

Z represents a carbon atom; and

R<sup>1</sup> is selected from hydrido and methyl; and

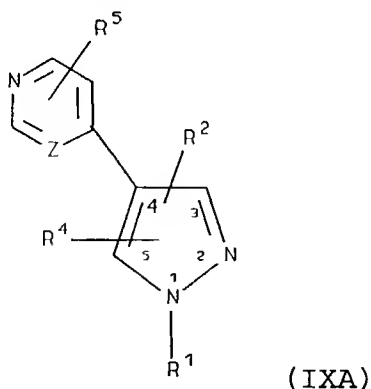
R<sup>2</sup> is hydrido; and

R<sup>4</sup> is selected from phenyl that is optionally substituted with one or more radicals independently selected from chloro, fluoro and bromo; and

R<sup>5</sup> is selected from hydrido and fluoro; or

a pharmaceutically-acceptable salt or tautomer thereof.

Within Formula IA there is another subclass of compounds of interest represented by Formula IXA:



wherein

Z represents a carbon atom or a nitrogen atom; and

R<sup>1</sup> is selected from hydrido, lower alkyl, lower hydroxyalkyl, lower alkynyl, lower aralkyl, lower aminoalkyl and lower alkylaminoalkyl; and

R<sup>2</sup> is selected from hydrido, lower alkylamino, lower alkynylamino, arylamino, lower aralkylamino, lower heterocyclylalkylamino, lower aminoalkylamino, lower alkylaminoalkylamino, lower hydroxyalkylamino, lower carboxyalkylamino, and lower alkoxyalkylamino, lower alkoxycarbonylaminoalkylamino, wherein the aryl group is optionally substituted with one or more radicals independently selected from halo, keto, lower alkyl, aralkyl, carboxy, lower alkoxy, lower alkylaminoalkylamino, lower alkynylamino, lower heterocyclylalkylamino, lower alkylcarbonyl and lower alkoxycarbonyl; or

R<sup>2</sup> is R<sup>200</sup>-heterocyclyl-R<sup>201</sup> or R<sup>200</sup>-cycloalkyl-R<sup>201</sup> wherein:

R<sup>200</sup> is selected from:

- (CR<sup>202</sup>R<sup>203</sup>)<sub>y</sub>-;

-NR<sup>202</sup>-;

-NR<sup>202</sup>-(CH<sub>2</sub>)<sub>y</sub>-;

-(CH<sub>2</sub>)<sub>y</sub>-NR<sup>202</sup>-;

-O-(CH<sub>2</sub>)<sub>y</sub>-;

-(CH<sub>2</sub>)<sub>y</sub>-O-;

-S-;

-O-;

or R<sup>200</sup> represents a bond;

R<sup>201</sup> represents one or more radicals selected from the group consisting of hydrido, halogen, hydroxy, carboxy, keto, lower alkyl, lower hydroxyalkyl, lower haloalkyl, lower cycloalkyl, lower alkenyl, lower alkynyl, aryl, heterocyclyl, lower aralkyl, lower heterocyclylalkylene, lower alkylcarbonyl, lower hydroxyalkylcarbonyl, lower cycloalkylcarbonyl,

arylcarbonyl, haloarylcarbonyl, lower alkoxy, lower alkoxyalkylene, lower alkoxyarylene, lower alkoxycarbonyl, lower carboxyalkylcarbonyl, lower alkoxyalkylcarbonyl, lower heterocyclylalkylcarbonyl, 5 lower alkylsulfonyl, lower alkylsulfonylalkylene, amino, lower aminoalkyl, lower alkylamino, lower aralkylamino, lower alkylaminoalkylene, aminocarbonyl, lower alkylcarbonylamino, lower alkylcarbonylaminoalkylene, lower alkylaminoalkylcarbonyl, lower 10 alkylaminoalkylcarbonylamino, lower aminoalkylcarbonylaminoalkyl, lower alkoxycarbonylamino, lower alkoxyalkylcarbonylamino, lower alkoxycarbonylaminoalkylene, lower alkylimidocarbonyl, amidino, lower alkylamidino, lower aralkylamidino, 15 guanidino, lower guanidinoalkylene, and lower alkylsulfonylamino; and

$R^{202}$  and  $R^{203}$  are independently selected from hydrido, lower alkyl, aryl and lower aralkyl; and

y is 0, 1, 2 or 3; and

20  $R^4$  is selected from aryl selected from phenyl, biphenyl, naphthyl, wherein said aryl is optionally substituted at a substitutable position with one or more radicals independently selected from halo, lower alkyl, lower alkoxy, aryloxy, lower aralkoxy, lower haloalkyl, 25 lower alkylthio, lower alkylamino, nitro, and hydroxy; and

$R^5$  is selected from hydrido, halo, amino, cyano, aminocarbonyl, lower alkyl, lower alkoxy, hydroxy, lower aminoalkyl, lower aralkyl, lower aralkyloxy, lower 30 aralkylamino, lower alkoxycarbonyl, lower alkylamino, lower hydroxyalkylamino, lower alkylcarbonyl, lower aralkenyl, lower arylheterocyclyl, carboxy, lower cycloalkylamino, lower hydroxycycloalkylamino, lower alkoxycarbonylamino, lower alkoxyaralkylamino, lower 35 alkylaminoalkylamino, lower heterocyclylamino, lower heterocyclylalkylamino, lower aralkylheterocyclylamino,

lower alkylaminocarbonyl, lower alkylcarbonyl, lower alkoxyaralkylamino, hydrazinyl, and lower alkylhydrazinyl, or  $-NR^{62}R^{63}$  wherein  $R^{62}$  is lower alkylcarbonyl or amino, and  $R^{63}$  is lower alkyl or lower phenylalkyl; or

a pharmaceutically-acceptable salt or tautomer thereof.

When the substituent at the 4-position of the pyrazole ring is a substituted pyridinyl, at least one of the substituents preferably is attached to a ring carbon atom adjacent the nitrogen heteroatom of the pyridine ring. When the substituent at the 4-position of the pyrazole ring is a substituted pyrimidinyl, at least one of the substituents preferably is attached to the carbon ring atom between the nitrogen heteroatoms of the pyrimidine ring. When  $R^2$  comprises a substituted piperidinyl or piperazinyl moiety, at least one of the substituents preferably is attached to the distal nitrogen heteroatom or to a carbon ring atom adjacent to the distal nitrogen heteroatom of the piperidine or piperazine ring.

A subclass of compounds of specific interest consists of those compounds of Formula IXA wherein:

$R^1$  is selected from hydrido, methyl, ethyl, hydroxyethyl and propargyl; and

$R^2$  is selected from hydrido, N-methylamino, N,N-dimethylamino, N-ethylamino, N,N-diethylamino, N-propylamino, N,N-dipropylamino, N-butylamino, N-propargylamino, N-phenylamino, N-benzylamino, aminoethylamino, aminopropylamino, aminobutylamino, methylaminoethylamino, dimethylaminoethylamino, ethylaminoethylamino, diethylaminoethylamino, methylaminopropylamino, dimethylaminopropylamino, ethylaminopropylamino, diethylaminopropylamino, morpholinylmethylamino, morpholinylethylamino,



morpholinylpropylamino, piperidinylmethylamino,  
piperidinylethylamino, piperidinylpropylamino,  
piperazinylmethylamino, piperazinylethylamino,  
piperazinylpropylamino, carboxymethylamino,  
5 carboxyethylamino, methoxyethylamino, ethoxyethylamino,  
ethoxymethylamino, (1,1-  
dimethyl)ethylcarbonylaminoethylamino, and (1,1-  
dimethyl)ethylcarbonylaminoethylamino, wherein the  
phenyl, morpholinyl, piperidinyl, and piperazinyl groups  
10 are optionally substituted with one or more radicals  
independently selected from fluoro, chloro, bromo, keto,  
methyl, ethyl, trifluoromethyl, benzyl, methoxy, ethoxy,  
methoxycarbonyl, ethoxycarbonyl and (1,1-  
dimethyl)ethoxycarbonyl; and

15  $R^2$  is  $R^{200}$ -piperidinyl- $R^{201}$ ,  $R^{200}$ -piperazinyl- $R^{201}$ , or  
 $R^{200}$ -cyclohexyl- $R^{201}$  wherein:

$R^{200}$  is selected from:

- $(CR^{202}R^{203})_y$ -;

- $NR^{202}$ -;

20 -S-;

-O-;

or  $R^{200}$  represents a bond;

$R^{201}$  represents one or more radicals selected from  
the group consisting of hydrido, chloro, fluoro, bromo,  
25 iodo, hydroxy, carboxy, keto, methyl, ethyl, propyl,  
butyl, hydroxymethyl, hydroxyethyl, hydroxypropyl,  
hydroxybutyl, (1-hydroxy-1,1-dimethyl)ethyl,  
chloromethyl, chloroethyl, chloropropyl, chlorobutyl,  
fluoromethyl, fluoroethyl, fluoropropyl, fluorobutyl,  
30 cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,  
ethenyl, propenyl, butenyl, ethynyl, propynyl, propargyl,  
butynyl, phenyl, benzyl, piperidinyl, piperazinyl,  
morpholinyl, piperidinylmethylene, piperazinylmethylene,  
morpholinylmethylene, methoxy, ethoxy, propoxy, butoxy,  
35 methoxymethylene, methoxyethylene, methoxypropylene,  
ethoxyethylene, ethoxypropylene, propoxyethylene,

propoxypropylene, methoxyphenylene, ethoxyphenylene,  
propoxyphenylene, methylcarbonyl, ethylcarbonyl,  
propylcarbonyl, cyclopropylcarbonyl, cyclobutylcarbonyl,  
cyclopentylcarbonyl, cyclohexylcarbonyl, benzoyl,  
5 chlorobenzoyl, fluorobenzoyl, hydroxymethylcarbonyl,  
hydroxyethylcarbonyl, hydroxypropylcarbonyl,  
carboxymethylcarbonyl, carboxyethylcarbonyl,  
carboxypropylcarbonyl, methoxymethylcarbonyl,  
methoxyethylcarbonyl, methoxypropylcarbonyl,  
10 ethoxymethylcarbonyl, ethoxyethylcarbonyl,  
ethoxypropylcarbonyl, propoxymethylcarbonyl,  
propoxyethylcarbonyl, propoxypropylcarbonyl,  
methoxyphenylcarbonyl, ethoxyphenylcarbonyl,  
propoxyphenylcarbonyl, piperidinylmethylcarbonyl,  
15 piperazinylmethylcarbonyl, morpholinylcarbonyl,  
methylsulfonyl, ethylsulfonyl, methylsulfonylmethylene,  
amino, aminomethyl, aminoethyl, aminopropyl, N-  
methylamino, N,N-dimethylamino, N-ethylamino, N,N-  
diethylamino, N-propylamino, N,N-dipropylamino,  
20 phenylamino, benzylamino, methylaminomethylene,  
ethylaminomethylene, methylaminoethylene,  
ethylaminoethylene, aminocarbonyl, methylcarbonylamino,  
ethylcarbonylamino, methylaminomethylcarbonyl,  
ethylaminomethylcarbonyl, methylcarbonylaminomethylene,  
25 ethylcarbonylaminomethylene,  
aminomethylcarbonylaminoethylmethylene,  
methoxycarbonylamino, ethoxycarbonylamino,  
methoxymethylcarbonylamino, methoxyethylcarbonylamino,  
ethoxymethylcarbonylamino, ethoxyethylcarbonylamino,  
30 methoxycarbonylaminomethylene,  
ethoxycarbonylaminomethylene, methylimidocarbonyl,  
ethylimidocarbonyl, amidino, methylamidino,  
methylamidino, benzylamidino, guanidino,  
guanidinomethylene, guanidinoethylene, and  
35 methylsulfonylamino; and

$R^{202}$  and  $R^{203}$  are independently selected from hydrido,

methyl, ethyl, propyl, butyl, phenyl and benzyl; and  
y is 0, 1 or 2; and

R<sup>4</sup> is phenyl, wherein said phenyl is optionally  
substituted with one or more radicals independently  
5 selected from methylthio, fluoro, chloro, bromo, iodo,  
methyl, ethyl, methoxy, ethoxy, phenoxy, benzyloxy,  
trifluoromethyl, nitro, dimethylamino, and hydroxy; and

R<sup>5</sup> is selected from hydrido, fluoro, chloro, bromo,  
iodo, hydroxy, methyl, ethyl, propyl, benzyl,

10 fluorophenylethyl, fluorophenylethenyl,  
fluorophenylpyrazolyl, cyano, carboxy, methoxy,  
methoxycarbonyl, aminocarbonyl, acetyl, methylamino,  
dimethylamino, 2-methylbutylamino, ethylamino,  
dimethylaminoethylamino, hydroxyethylamino,  
15 hydroxypropylamino, hydroxybutylamino,  
hydroxycyclopropylamino, hydroxycyclobutylamino,  
hydroxycyclopentylamino, hydroxycyclohexylamino,  
imidazolylamino, morpholinylethylamino, (1-ethyl-2-  
hydroxy)ethylamino, piperidinylamino,

20 pyridinylmethylamino, phenylmethylpiperidinylamino,  
aminomethyl, cyclopropylamino, amino, hydroxy,  
ethoxycarbonylamino, methoxyphenylmethylamino,  
phenylmethylamino, fluorophenylmethylamino,  
fluorophenylethylamino, methylaminoethylamino,

25 dimethylaminoethylamino, methylaminopropylamino,  
dimethylaminopropylamino, methylaminobutylamino,  
dimethylaminobutylamino, methylaminopentylamino,  
dimethylaminopentylamino, ethylaminoethylamino,  
diethylaminoethylamino, ethylaminopropylamino,  
30 diethylaminopropylamino, ethylaminobutylamino,  
diethylaminobutylamino, ethylaminopentylamino,

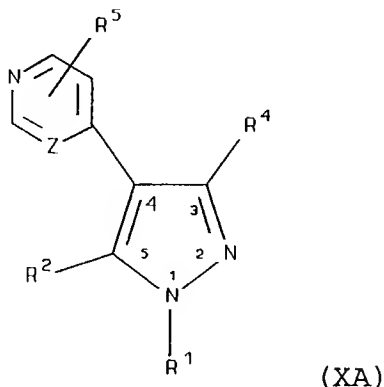
methylaminocarbonyl, methylcarbonyl, ethylcarbonyl,  
hydrazinyl, and 1-methylhydrazinyl, or -NR<sup>62</sup>R<sup>63</sup> wherein R<sup>62</sup>  
is methylcarbonyl or amino, and R<sup>63</sup> is methyl or benzyl;

35 or

a pharmaceutically-acceptable salt or tautomer

thereof.

Within Formula IXA there is another subclass of compounds of interest represented by Formula XA:



wherein:

$R^1$  is selected from hydrido, methyl, ethyl, hydroxyethyl and propargyl; and

$R^2$  is selected from hydrido, N-methylamino, N,N-dimethylamino, N-ethylamino, N,N-diethylamino, N-propylamino, N,N-dipropylamino, N-butylamino, N-propargylamino, N-phenylamino, N-benzylamino, aminoethylamino, aminopropylamino, aminobutylamino, methylaminoethylamino, dimethylaminoethylamino, ethylaminoethylamino, diethylaminoethylamino, methylaminopropylamino, dimethylaminopropylamino, ethylaminopropylamino, diethylaminopropylamino, morpholinylmethylamino, morpholinylethylamino, morpholinylpropylamino, piperidinylmethylamino, piperidinylethylamino, piperidinylpropylamino, piperazinylmethylamino, piperazinylethylamino, and piperazinylpropylamino, wherein the phenyl, morpholinyl, piperidinyl, and piperazinyl groups are optionally substituted with one or more radicals independently selected from fluoro, chloro, bromo, keto, methyl, ethyl,

trifluoromethyl, benzyl, and methoxy; and

R<sup>4</sup> is phenyl, wherein said phenyl is optionally substituted with one or more radicals independently selected from fluoro, chloro, methyl, ethyl, methoxy and  
5 ethoxy; and

R<sup>5</sup> is selected from hydrido, fluoro, chloro, bromo, hydroxy, methyl, ethyl, propyl, benzyl, cyano, carboxy, methoxy, methoxycarbonyl, aminocarbonyl, acetyl, methylamino, dimethylamino, 2-methylbutylamino,  
10 ethylamino, dimethylaminoethylamino, hydroxyethylamino, hydroxypropylamino, hydroxybutylamino, hydroxycyclopropylamino, hydroxycyclobutylamino, hydroxycyclopentylamino, hydroxycyclohexylamino, imidazolylamino, morpholinylethylamino, (1-ethyl-2-  
15 hydroxy)ethylamino, piperidinylamino, pyridinylmethylamino, phenylmethylpiperidinylamino, aminomethyl, cyclopropylamino, amino, hydroxy, ethoxycarbonylamino, methoxyphenylmethylamino, phenylmethylamino, fluorophenylmethylamino,  
20 fluorophenylethylamino, methylaminoethylamino, dimethylaminoethylamino, methylaminopropylamino, dimethylaminopropylamino, methylaminobutylamino, dimethylaminobutylamino, methylaminopentylamino, dimethylaminopentylamino, ethylaminoethylamino,  
25 diethylaminoethylamino, ethylaminopropylamino, diethylaminopropylamino, ethylaminobutylamino, diethylaminobutylamino, ethylaminopentylamino, methylaminocarbonyl, methylcarbonyl, and ethylcarbonyl;  
or

30 a pharmaceutically-acceptable salt or tautomer thereof.

A subclass of compounds of particular interest consists of those compounds of Formula XA wherein:

R<sup>1</sup> is selected from hydrido, methyl, ethyl,  
35 hydroxyethyl and propargyl; and

R<sup>2</sup> is selected from hydrido, methylaminopropylamino,

dimethylaminopropylamino, ethylaminopropylamino, diethylaminopropylamino, morpholinylmethylamino, morpholinylethylamino, morpholinylpropylamino, wherein the phenyl and morpholinyl groups are optionally  
5 substituted with one or more radicals independently selected from fluoro, chloro, bromo, methyl, ethyl, and methoxy; and

R<sup>4</sup> is phenyl, wherein said phenyl is optionally substituted with one or more radicals independently  
10 selected from fluoro, chloro, methyl, ethyl, methoxy and ethoxy; and

R<sup>5</sup> is selected from hydrido, fluoro, chloro, bromo, hydroxy, methyl, ethyl, cyano, carboxy, methoxy, methoxycarbonyl, aminocarbonyl, acetyl, methylamino,  
15 dimethylamino, ethylamino, dimethylaminoethylamino, hydroxyethylamino, hydroxypropylamino, hydroxybutylamino, hydroxycyclopropylamino, hydroxycyclobutylamino, hydroxycyclopentylamino, hydroxycyclohexylamino, (1-ethyl-2-hydroxy)ethylamino, aminomethyl,  
20 cyclopropylamino, amino, ethoxycarbonylamino, methoxyphenylmethylamino, phenylmethylamino, fluorophenylmethylamino, fluorophenylethylamino, methylaminoethylamino, dimethylaminoethylamino, methylaminopropylamino, dimethylaminopropylamino,  
25 methylaminobutylamino, dimethylaminobutylamino, methylaminopentylamino, dimethylaminopentylamino, ethylaminoethylamino, diethylaminoethylamino, ethylaminopropylamino, diethylaminopropylamino, ethylaminobutylamino, diethylaminobutylamino,  
30 ethylaminopentylamino, methylaminocarbonyl, methylcarbonyl, and ethylcarbonyl; or

a pharmaceutically-acceptable salt or tautomer thereof.

35 A subclass of compounds of specific interest consists of those compounds of Formula XA wherein:

R<sup>1</sup> is hydrido; and

R<sup>2</sup> is selected from hydrido, methylaminopropylamino, dimethylaminopropylamino, ethylaminopropylamino, diethylaminopropylamino, morpholinylmethylamino,

5 morpholinylethylamino, and morpholinylpropylamino; and

R<sup>4</sup> is phenyl, wherein said phenyl is optionally substituted with one or more radicals independently selected from fluoro, chloro, methyl, and methoxy; and

R<sup>5</sup> is selected from hydrido, methylamino,  
10 dimethylamino, ethylamino, dimethylaminoethylamino, hydroxypropylamino, hydroxyethylamino, hydroxypropylamino, hydroxybutylamino, hydroxycyclopropylamino, hydroxycyclobutylamino, hydroxycyclopentylamino, hydroxycyclohexylamino, (1-ethyl-2-hydroxy)ethylamino, aminomethyl,  
15 cyclopropylamino, amino, dimethylaminoethylamino, dimethylaminopropylamino, dimethylaminobutylamino, dimethylaminopentylamino, diethylaminoethylamino, diethylaminopropylamino, diethylaminobutylamino, and  
20 diethylaminopentylamino; or

a pharmaceutically-acceptable salt or tautomer thereof.

A subclass of compounds of high interest consists of those compounds of Formula XA wherein:

25 R<sup>1</sup> is selected hydrido; and

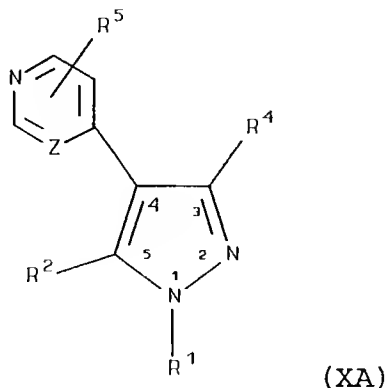
R<sup>2</sup> is selected from hydrido, dimethylaminopropylamino, diethylaminopropylamino, morpholinylethylamino, and morpholinylpropylamino; and

R<sup>4</sup> is phenyl, wherein said phenyl is optionally  
30 substituted with one or more radicals independently selected from fluoro, chloro, methyl, and methoxy; and

R<sup>5</sup> is selected from hydrido, hydroxypropylamino, hydroxycyclohexylamino, diethylaminoethylamino; or

a pharmaceutically-acceptable salt or tautomer  
35 thereof.

Within Formula IA there is another subclass of compounds of interest represented by Formula XA:



$R^1$  is selected from hydrido, methyl, ethyl,  
5 hydroxyethyl and propargyl; and

$R^2$  is  $R^{200}$ -piperidinyl- $R^{201}$  wherein:

$R^{200}$  is selected from:

-  $(CR^{202}R^{203})_y$ -;

-  $NR^{202}$ -;

10 -S-;

-O-;

or  $R^{200}$  represents a bond;

$R^{201}$  represents one or more radicals selected from  
the group consisting of hydrido, chloro, fluoro, bromo,  
15 iodo, hydroxy, carboxy, keto, methyl, ethyl, propyl,  
butyl, hydroxymethyl, hydroxyethyl, hydroxypropyl,  
hydroxybutyl, (1-hydroxy-1,1-dimethyl)ethyl,  
chloromethyl, chloroethyl, chloropropyl, chlorobutyl,  
fluoromethyl, fluoroethyl, fluoropropyl, fluorobutyl,  
20 cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,  
ethenyl, propenyl, butenyl, ethynyl, propynyl, propargyl,  
butynyl, phenyl, benzyl, piperidinyl, piperazinyl,  
morpholinyl, piperidinylmethylene, piperazinylmethylene,  
morpholinylmethylene, methoxy, ethoxy, propoxy, butoxy,  
25 methoxymethylene, methoxyethylene, methoxypropylene,



ethoxyethylene, ethoxypropylene, propoxyethylene,  
propoxypropylene, methoxyphenylene, ethoxyphenylene,  
propoxyphenylene, methylcarbonyl, ethylcarbonyl,  
propylcarbonyl, cyclopropylcarbonyl, cyclobutylcarbonyl,  
5 cyclopentylcarbonyl, cyclohexylcarbonyl, benzoyl,  
chlorobenzoyl, fluorobenzoyl, hydroxymethylcarbonyl,  
hydroxyethylcarbonyl, hydroxypropylcarbonyl,  
carboxymethylcarbonyl, carboxyethylcarbonyl,  
carboxypropylcarbonyl, methoxymethylcarbonyl,  
10 methoxyethylcarbonyl, methoxypropylcarbonyl,  
ethoxymethylcarbonyl, ethoxyethylcarbonyl,  
ethoxypropylcarbonyl, propoxymethylcarbonyl,  
propoxyethylcarbonyl, propoxypropylcarbonyl,  
methoxyphenylcarbonyl, ethoxyphenylcarbonyl,  
15 propoxyphenylcarbonyl, piperidinylmethylcarbonyl,  
piperazinylmethylcarbonyl, morpholinylcarbonyl,  
methylsulfonyl, ethylsulfonyl, methylsulfonylmethylene,  
amino, aminomethyl, aminoethyl, aminopropyl, N-  
methylamino, N,N-dimethylamino, N-ethylamino, N,N-  
20 diethylamino, N-propylamino, N,N-dipropylamino,  
phenylamino, benzylamino, methylaminomethylene,  
ethylaminomethylene, methylaminoethylene,  
ethylaminoethylene, aminocarbonyl, methylcarbonylamino,  
ethylcarbonylamino, methylaminomethylcarbonyl,  
25 ethylaminomethylcarbonyl, methylcarbonylaminomethylene,  
ethylcarbonylaminomethylene,  
aminomethylcarbonylaminoethylmethylene,  
methoxycarbonylamino, ethoxycarbonylamino,  
methoxymethylcarbonylamino, methoxyethylcarbonylamino,  
30 ethoxymethylcarbonylamino, ethoxyethylcarbonylamino,  
methoxycarbonylaminomethylene,  
ethoxycarbonylaminomethylene, methylimidocarbonyl,  
ethylimidocarbonyl, amidino, methylamidino,  
methylamidino, benzylamidino, guanidino,  
35 guanidinomethylene, guanidinoethylene, and  
methylsulfonylamino; and

$R^{202}$  and  $R^{203}$  are independently selected from hydrido, methyl, ethyl, propyl, butyl, phenyl and benzyl; and

y is 0, 1 or 2; and

5  $R^4$  is phenyl, wherein said phenyl is optionally substituted with one or more radicals independently selected from fluoro, chloro, methyl, ethyl, methoxy and ethoxy; and

$R^5$  is selected from hydrido, fluoro, chloro, bromo,  
10 hydroxy, methyl, ethyl, propyl, benzyl, cyano, carboxy, methoxy, methoxycarbonyl, aminocarbonyl, acetyl, methylamino, dimethylamino, 2-methylbutylamino, ethylamino, dimethylaminoethylamino, hydroxyethylamino, hydroxypropylamino, hydroxybutylamino,  
15 hydroxycyclopropylamino, hydroxycyclobutylamino, hydroxycyclopentylamino, hydroxycyclohexylamino, imidazolylamino, morpholinylethylamino, (1-ethyl-2-hydroxy)ethylamino, piperidinylamino, pyridinylmethylamino, phenylmethylpiperidinylamino,  
20 aminomethyl, cyclopropylamino, amino, hydroxy, ethoxycarbonylamino, methoxyphenylmethylamino, phenylmethylamino, fluorophenylmethylamino, fluorophenylethylamino, methylaminoethylamino, dimethylaminoethylamino, methylaminopropylamino,  
25 dimethylaminopropylamino, methylaminobutylamino, dimethylaminobutylamino, methylaminopentylamino, dimethylaminopentylamino, ethylaminoethylamino, diethylaminoethylamino, ethylaminopropylamino, diethylaminopropylamino, ethylaminobutylamino,  
30 diethylaminobutylamino, ethylaminopentylamino, methylaminocarbonyl, methylcarbonyl, and ethylcarbonyl;  
or

a pharmaceutically-acceptable salt or tautomer thereof.

35 A subclass of compounds of particular interest

consists of those compounds of Formula XA wherein:

$R^1$  is selected from hydrido, methyl, ethyl, hydroxyethyl and propargyl; and

$R^2$  is  $R^{200}$ -piperidinyl- $R^{201}$  wherein:

5  $R^{200}$  is selected from:

methylene;

- $NR^{202}$ -;

-S-;

-O-;

10 or  $R^{200}$  represents a bond;

$R^{201}$  represents one or more radicals selected from the group consisting of hydrido, chloro, fluoro, hydroxy, carboxy, keto, methyl, ethyl, propyl, hydroxymethyl, hydroxyethyl, hydroxypropyl, (1-hydroxy-1,1-dimethyl)ethyl, chloromethyl, chloroethyl, chloropropyl, 15 fluoromethyl, fluororoethyl, fluoropropyl, phenyl, benzyl, piperidinyl, piperazinyl, morpholinyl, piperidinylmethylene, piperazinylmethylene, morpholinylmethylene, methoxy, ethoxy, propoxy, 20 methoxymethyl, methoxyethyl, methoxypropyl, ethoxyethyl, ethoxypropyl, propoxyethyl, propoxypropyl, methoxyphenyl, ethoxyphenyl, propoxyphenyl, methylcarbonyl, ethylcarbonyl, propylcarbonyl, hydroxymethylcarbonyl, hydroxyethylcarbonyl, carboxymethylcarbonyl, 25 carboxyethylcarbonyl, methoxymethylcarbonyl, methoxyethylcarbonyl, methoxypropylcarbonyl, ethoxymethylcarbonyl, ethoxyethylcarbonyl, ethoxypropylcarbonyl, propoxymethylcarbonyl, propoxyethylcarbonyl, propoxypropylcarbonyl, 30 methoxyphenylcarbonyl, ethoxyphenylcarbonyl, propoxyphenylcarbonyl, methylsulfonyl, ethylsulfonyl, methylsulfonylmethylene, amino, aminomethyl, aminoethyl, aminopropyl, N-methylamino, N,N-dimethylamino, N-ethylamino, N,N-diethylamino, N-propylamino, N,N-dipropylamino, N-benzylamino, methylaminomethylene, 35 aminocarbonyl, methoxycarbonylamino, ethoxycarbonylamino,

or methylsulfonylamino; and

$R^{202}$  is selected from hydrido, methyl, ethyl, phenyl and benzyl; and

$R^4$  is phenyl, wherein said phenyl is optionally  
5 substituted with one or more radicals independently selected from fluoro, chloro, methyl, ethyl, methoxy and ethoxy; and

$R^5$  is selected from hydrido, fluoro, chloro, bromo, hydroxy, methyl, ethyl, cyano, carboxy, methoxy,  
10 methoxycarbonyl, aminocarbonyl, acetyl, methylamino, dimethylamino, ethylamino, dimethylaminoethylamino, hydroxyethylamino, hydroxypropylamino, hydroxybutylamino, hydroxycyclopropylamino, hydroxycyclobutylamino, hydroxycyclopentylamino, hydroxycyclohexylamino, (1-ethyl-2-hydroxy)ethylamino, aminomethyl,  
15 cyclopropylamino, amino, ethoxycarbonylamino, methoxyphenylmethylamino, phenylmethylamino, fluorophenylmethylamino, fluorophenylethylamino, methylaminoethylamino, dimethylaminoethylamino, methylaminopropylamino, dimethylaminopropylamino, methylaminobutylamino, dimethylaminobutylamino, methylaminopentylamino, dimethylaminopentylamino, ethylaminoethylamino, diethylaminoethylamino, ethylaminopropylamino, diethylaminopropylamino,  
20 ethylaminobutylamino, diethylaminobutylamino, ethylaminopentylamino, methylaminocarbonyl, methylcarbonyl, and ethylcarbonyl; or

a pharmaceutically-acceptable salt or tautomer thereof.

30

A subclass of compounds of specific interest consists of those compounds of Formula XA wherein:

$R^1$  is hydrido; and

$R^2$  is  $R^{200}$ -piperidinyl- $R^{201}$  wherein:

35  $R^{200}$  is selected from:

methylene;

-NR<sup>202</sup>-;

-S-;

-O-;

or R<sup>200</sup> represents a bond;

5       R<sup>201</sup> represents one or more radicals selected from  
the group consisting of hydrido, hydroxy, methyl, ethyl,  
propyl, hydroxymethyl, hydroxyethyl, hydroxypropyl,  
methoxymethyl, methoxyethyl, methoxypropyl, ethoxyethyl,  
ethoxypropyl, propoxyethyl, propoxypropyl, methoxyphenyl,  
10   ethoxyphenyl, propoxyphenyl, methylcarbonyl,  
ethylcarbonyl, propylcarbonyl, hydroxymethylcarbonyl,  
hydroxyethylcarbonyl, carboxymethylcarbonyl,  
carboxyethylcarbonyl, methoxymethylcarbonyl,  
methoxyethylcarbonyl, ethoxymethylcarbonyl,  
15   ethoxyethylcarbonyl, methoxyphenylcarbonyl,  
ethoxyphenylcarbonyl, methylsulfonyl, ethylsulfonyl,  
amino, aminomethyl, aminoethyl, aminopropyl, N-  
methylamino, N,N-dimethylamino, N-ethylamino, N,N-  
diethylamino, N-propylamino, N,N-dipropylamino, N-  
20   benzylamino, methylaminomethylene, aminocarbonyl,  
methoxycarbonylamino, and ethoxycarbonylamino; and

R<sup>202</sup> is selected from hydrido, methyl phenyl and  
benzyl; and

R<sup>4</sup> is phenyl, wherein said phenyl is optionally  
25   substituted with one or more radicals independently  
selected from fluoro, chloro, methyl, and methoxy; and

R<sup>5</sup> is selected from hydrido, methylamino,  
dimethylamino, 2-methylbutylamino, ethylamino,  
dimethylaminoethylamino, hydroxypropylamino,  
30   hydroxyethylamino, hydroxypropylamino, hydroxybutylamino,  
hydroxycyclopropylamino, hydroxycyclobutylamino,  
hydroxycyclopentylamino, hydroxycyclohexylamino, (1-  
ethyl-2-hydroxy)ethylamino, aminomethyl,  
cyclopropylamino, amino, dimethylaminoethylamino,  
35   dimethylaminopropylamino, dimethylaminobutylamino,  
dimethylaminopentylamino, diethylaminoethylamino,

diethylaminopropylamino, diethylaminobutylamino, and diethylaminopentylamino; or

a pharmaceutically-acceptable salt or tautomer thereof.

5

A subclass of compounds of high interest consists of those compounds of Formula XA wherein:

$R^1$  is hydrido; and

$R^2$  is  $R^{200}$ -piperidiny- $R^{201}$  wherein:

10 

$R^{200}$  is selected from:

methylene;

$-NR^{202}-$ ;

$-S-$ ;

$-O-$ ;

15 

or  $R^{200}$  represents a bond;

$R^{201}$  represents one or more radicals selected from the group consisting of hydrido, methyl, methoxyethyl, methylcarbonyl, hydroxymethylcarbonyl, methoxymethylcarbonyl, methylsulfonyl, amino, N,N-dimethylamino, and N,N-diethylamino; and

20

$R^{202}$  is selected from hydrido and methyl; and

$R^4$  is phenyl, wherein said phenyl is optionally substituted with one or more radicals independently selected from fluoro, chloro, methyl, and methoxy; and

25

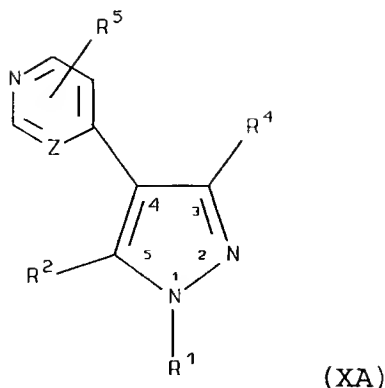
$R^5$  is selected from hydrido, hydroxypropylamino, hydroxycyclohexylamino, diethylaminoethylamino; or

a pharmaceutically-acceptable salt or tautomer thereof.

30

Within Formula IXA there is another subclass of compounds of interest represented by Formula XA:

104



$R^1$  is selected from hydrido, methyl, ethyl, hydroxyethyl and propargyl; and

$R^2$  is  $R^{200}$ -piperazinyl- $R^{201}$  wherein:

5  $R^{200}$  is selected from:

-  $(CR^{202}R^{203})_y$ -;

- $NR^{202}$ -;

-S-;

-O-;

10 or  $R^{200}$  represents a bond;

$R^{201}$  represents one or more radicals selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, hydroxy, carboxy, keto, methyl, ethyl, propyl, butyl, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, (1-hydroxy-1,1-dimethyl)ethyl, chloromethyl, chloroethyl, chloropropyl, chlorobutyl, fluoromethyl, fluoroethyl, fluoropropyl, fluorobutyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, ethenyl, propenyl, butenyl, ethynyl, propynyl, propargyl, butynyl, phenyl, benzyl, piperidinyl, piperazinyl, morpholinyl, piperidinylmethylene, piperazinylmethylene, morpholinylmethylene, methoxy, ethoxy, propoxy, butoxy, methoxymethylene, methoxyethylene, methoxypropylene, ethoxyethylene, ethoxypropylene, propoxyethylene, propoxypropylene, methoxyphenylene, ethoxyphenylene,

25

propoxyphenylene, methylcarbonyl, ethylcarbonyl, propylcarbonyl, cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, benzoyl, chlorobenzoyl, fluorobenzoyl, hydroxymethylcarbonyl, hydroxyethylcarbonyl, hydroxypropylcarbonyl, carboxymethylcarbonyl, carboxyethylcarbonyl, carboxypropylcarbonyl, methoxymethylcarbonyl, methoxyethylcarbonyl, methoxypropylcarbonyl, ethoxymethylcarbonyl, ethoxyethylcarbonyl, ethoxypropylcarbonyl, propoxymethylcarbonyl, propoxyethylcarbonyl, propoxypropylcarbonyl, methoxyphenylcarbonyl, ethoxyphenylcarbonyl, propoxyphenylcarbonyl, piperidinylmethylcarbonyl, piperazinylmethylcarbonyl, morpholinylcarbonyl, methylsulfonyl, ethylsulfonyl, methylsulfonylmethylene, amino, aminomethyl, aminoethyl, aminopropyl, N-methylamino, N,N-dimethylamino, N-ethylamino, N,N-diethylamino, N-propylamino, N,N-dipropylamino, phenylamino, benzylamino, methylaminomethylene, ethylaminomethylene, methylaminoethylene, ethylaminoethylene, aminocarbonyl, methylcarbonylamino, ethylcarbonylamino, methylaminomethylcarbonyl, ethylaminomethylcarbonyl, methylcarbonylaminomethylene, ethylcarbonylaminomethylene, aminomethylcarbonylaminocarbonylmethylene, methoxycarbonylamino, ethoxycarbonylamino, methoxymethylcarbonylamino, methoxyethylcarbonylamino, ethoxymethylcarbonylamino, ethoxyethylcarbonylamino, methoxycarbonylaminomethylene, ethoxycarbonylaminomethylene, methylimidocarbonyl, ethylimidocarbonyl, amidino, methylamidino, methylamidino, benzylamidino, guanidino, guanidinomethylene, guanidinoethylene, and methylsulfonylamino; and

$R^{202}$  and  $R^{203}$  are independently selected from hydrido, methyl, ethyl, propyl, butyl, phenyl and benzyl; and



y is 0, 1 or 2; and

R<sup>4</sup> is phenyl, wherein said phenyl is optionally substituted with one or more radicals independently selected from fluoro, chloro, methyl, ethyl, methoxy and  
5 ethoxy; and

R<sup>5</sup> is selected from hydrido, fluoro, chloro, bromo, hydroxy, methyl, ethyl, propyl, benzyl, cyano, carboxy, methoxy, methoxycarbonyl, aminocarbonyl, acetyl, methylamino, dimethylamino, 2-methylbutylamino,  
10 ethylamino, dimethylaminoethylamino, hydroxyethylamino, hydroxypropylamino, hydroxybutylamino, hydroxycyclopropylamino, hydroxycyclobutylamino, hydroxycyclopentylamino, hydroxycyclohexylamino, imidazolylamino, morpholinylethylamino, (1-ethyl-2-  
15 hydroxy)ethylamino, piperidinylamino, pyridinylmethylamino, phenylmethylpiperidinylamino, aminomethyl, cyclopropylamino, amino, hydroxy, ethoxycarbonylamino, methoxyphenylmethylamino, phenylmethylamino, fluorophenylmethylamino,  
20 fluorophenylethylamino, methylaminoethylamino, dimethylaminoethylamino, methylaminopropylamino, dimethylaminopropylamino, methylaminobutylamino, dimethylaminobutylamino, methylaminopentylamino, dimethylaminopentylamino, ethylaminoethylamino,  
25 diethylaminoethylamino, ethylaminopropylamino, diethylaminopropylamino, ethylaminobutylamino, diethylaminobutylamino, ethylaminopentylamino, methylaminocarbonyl, methylcarbonyl, and ethylcarbonyl;  
or

30 a pharmaceutically-acceptable salt or tautomer thereof.

A subclass of compounds of particular interest consists of those compounds of Formula XA wherein:

35 R<sup>1</sup> is selected from hydrido, methyl, ethyl, hydroxyethyl and propargyl; and

$R^2$  is  $R^{200}$ -piperazinyl- $R^{201}$  wherein:

$R^{200}$  is selected from:

-  $(CR^{202}R^{203})_y$ -;

- $NR^{202}$ -;

5 -S-;

-O-;

or  $R^{200}$  represents a bond;

$R^{201}$  represents one or more radicals selected from  
the group consisting of hydrido, chloro, fluoro, bromo,  
10 hydroxy, carboxy, keto, methyl, ethyl, propyl,  
hydroxymethyl, hydroxyethyl, hydroxypropyl, (1-hydroxy-  
1,1-dimethyl)ethyl, chloromethyl, chloroethyl,  
chloropropyl, fluoromethyl, fluoroethyl, fluoropropyl,  
cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,  
15 ethenyl, propenyl, butenyl, ethynyl, propynyl, propargyl,  
phenyl, benzyl, piperidinyl, piperazinyl, morpholinyl,  
piperidinylmethylene, piperazinylmethylene,  
morpholinylmethylene, methoxy, ethoxy, propoxy,  
methoxymethylene, methoxyethylene, ethoxyethylene,  
20 methoxyphenylene, ethoxyphenylene, methylcarbonyl,  
ethylcarbonyl, propylcarbonyl, cyclopropylcarbonyl,  
cyclobutylcarbonyl, cyclopentylcarbonyl,  
cyclohexylcarbonyl, benzoyl, chlorobenzoyl,  
fluorobenzoyl, hydroxymethylcarbonyl,  
25 hydroxyethylcarbonyl, hydroxypropylcarbonyl,  
carboxymethylcarbonyl, carboxyethylcarbonyl,  
carboxypropylcarbonyl, methoxymethylcarbonyl,  
methoxyethylcarbonyl, methoxypropylcarbonyl,  
ethoxymethylcarbonyl, ethoxyethylcarbonyl,  
30 ethoxypropylcarbonyl, propoxymethylcarbonyl,  
propoxyethylcarbonyl, propoxypropylcarbonyl,  
methoxyphenylcarbonyl, ethoxyphenylcarbonyl,  
propoxyphenylcarbonyl, piperidinylmethylcarbonyl,  
piperazinylmethylcarbonyl, morpholinylcarbonyl,  
35 methylsulfonyl, ethylsulfonyl, methylsulfonylmethylene,  
amino, aminomethyl, aminoethyl, aminopropyl, N-

methyamino, N,N-dimethylamino, N-ethylamino, N,N-diethylamino, N-propylamino, N,N-dipropylamino, phenylamino, benzylamino, methylaminomethylene, ethylaminomethylene, methylaminoethylene, ethylaminoethylene, aminocarbonyl, methylcarbonylamino, ethylcarbonylamino, methylaminomethylcarbonyl, ethylaminomethylcarbonyl, methylcarbonylaminomethylene, ethylcarbonylaminomethylene, aminomethylcarbonylaminoethylmethylene, methoxycarbonylamino, ethoxycarbonylamino, methoxymethylcarbonylamino, methoxyethylcarbonylamino, ethoxymethylcarbonylamino, ethoxyethylcarbonylamino, methoxycarbonylaminomethylene, ethoxycarbonylaminomethylene, and methylsulfonylamino; and

$R^{202}$  and  $R^{203}$  are independently selected from hydrido, methyl, ethyl, phenyl and benzyl; and

y is 0, 1 or 2; and

$R^4$  is phenyl, wherein said phenyl is optionally substituted with one or more radicals independently selected from fluoro, chloro, methyl, ethyl, methoxy and ethoxy; and

$R^5$  is selected from hydrido, fluoro, chloro, bromo, hydroxy, methyl, ethyl, cyano, carboxy, methoxy, methoxycarbonyl, aminocarbonyl, acetyl, methylamino, dimethylamino, ethylamino, dimethylaminoethylamino, hydroxyethylamino, hydroxypropylamino, hydroxybutylamino, hydroxycyclopropylamino, hydroxycyclobutylamino, hydroxycyclopentylamino, hydroxycyclohexylamino, (1-ethyl-2-hydroxy)ethylamino, aminomethyl, cyclopropylamino, amino, ethoxycarbonylamino, methoxyphenylmethylamino, phenylmethylamino, fluorophenylmethylamino, fluorophenylethylamino, methylaminoethylamino, dimethylaminoethylamino, methylaminopropylamino, dimethylaminopropylamino, methylaminobutylamino, dimethylaminobutylamino,

methylaminopentylamino, dimethylaminopentylamino,  
ethylaminoethylamino, diethylaminoethylamino,  
ethylaminopropylamino, diethylaminopropylamino,  
ethylaminobutylamino, diethylaminobutylamino,  
5 ethylaminopentylamino, methylaminocarbonyl,  
methylcarbonyl, and ethylcarbonyl; or  
a pharmaceutically-acceptable salt or tautomer  
thereof.

- 10 A subclass of compounds of specific interest  
consists of those compounds of Formula XA wherein:  
R<sup>1</sup> is hydrido; and  
R<sup>2</sup> is R<sup>200</sup>-piperazinyl-R<sup>201</sup> wherein:  
R<sup>200</sup> is selected from:  
15 methylene;  
-NR<sup>202</sup>-;  
-S-;  
-O-;  
or R<sup>200</sup> represents a bond;  
20 R<sup>201</sup> represents one or more radicals selected from  
the group consisting of hydrido, methyl, ethyl, propyl,  
cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,  
ethynyl, propynyl, propargyl, phenyl, benzyl,  
piperidinyl, piperazinyl, and morpholinyl; and  
25 R<sup>202</sup> is selected from hydrido, methyl, ethyl, phenyl  
and benzyl; and  
y is 0, 1 or 2; and  
R<sup>4</sup> is phenyl, wherein said phenyl is optionally  
substituted with one or more radicals independently  
30 selected from fluoro, chloro, methyl, and methoxy; and  
R<sup>5</sup> is selected from hydrido, methylamino,  
dimethylamino, 2-methylbutylamino, ethylamino,  
dimethylaminoethylamino, hydroxypropylamino,  
hydroxyethylamino, hydroxypropylamino, hydroxybutylamino,  
35 hydroxycyclopropylamino, hydroxycyclobutylamino,  
hydroxycyclopentylamino, hydroxycyclohexylamino, (1-

ethyl-2-hydroxy)ethylamino, aminomethyl,  
cyclopropylamino, amino, dimethylaminoethylamino,  
dimethylaminopropylamino, dimethylaminobutylamino,  
dimethylaminopentylamino, diethylaminoethylamino,  
5 diethylaminopropylamino, diethylaminobutylamino, and  
diethylaminopentylamino; or  
a pharmaceutically-acceptable salt or tautomer  
thereof.

10 A subclass of compounds of high interest consists of  
those compounds of Formula XA wherein:

R<sup>1</sup> is hydrido; and

R<sup>2</sup> is R<sup>200</sup>-piperaziny-<sup>1</sup>-R<sup>201</sup> wherein:

R<sup>200</sup> is selected from:

15 methylene;

-NR<sup>202</sup>-;

-S-;

-O-;

or R<sup>200</sup> represents a bond;

20 R<sup>201</sup> represents one or more radicals selected from  
the group consisting of hydrido, methyl, cyclopropyl,  
propargyl, and benzyl; and

R<sup>202</sup> is selected from hydrido and methyl; and

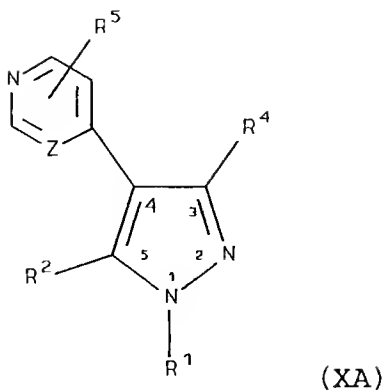
25 R<sup>4</sup> is phenyl, wherein said phenyl is optionally  
substituted with one or more radicals independently  
selected from fluoro, chloro, methyl, and methoxy; and

R<sup>5</sup> is selected from hydrido, hydroxypropylamino,  
hydroxycyclohexylamino, and diethylaminoethylamino; or

30 a pharmaceutically-acceptable salt or tautomer  
thereof.

Within Formula IA there is another subclass of  
compounds of interest represented by Formula XA:

111



$R^1$  is selected from hydrido, methyl, ethyl, hydroxyethyl and propargyl; and

$R^2$  is  $R^{200}$ -cyclohexyl- $R^{201}$  wherein:

5  $R^{200}$  is selected from:

-  $(CR^{202}R^{203})_y$ -;

- $NR^{202}$ -;

-S-;

-O-;

10 or  $R^{200}$  represents a bond;

$R^{201}$  represents one or more radicals selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, hydroxy, carboxy, keto, methyl, ethyl, propyl, butyl, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, (1-hydroxy-1,1-dimethyl)ethyl, chloromethyl, chloroethyl, chloropropyl, chlorobutyl, fluoromethyl, fluoroethyl, fluoropropyl, fluorobutyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, ethenyl, propenyl, butenyl, ethynyl, propynyl, propargyl, butynyl, phenyl, benzyl, piperidinyl, piperazinyl, morpholinyl, piperidinylmethylene, piperazinylmethylene, morpholinylmethylene, methoxy, ethoxy, propoxy, butoxy, methoxymethylene, methoxyethylene, methoxypropylene, ethoxyethylene, ethoxypropylene, propoxyethylene, propoxypropylene, methoxyphenylene, ethoxyphenylene,

25

propoxyphenylene, methylcarbonyl, ethylcarbonyl, propylcarbonyl, cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, benzoyl, chlorobenzoyl, fluorobenzoyl, hydroxymethylcarbonyl, hydroxyethylcarbonyl, hydroxypropylcarbonyl, carboxymethylcarbonyl, carboxyethylcarbonyl, carboxypropylcarbonyl, methoxymethylcarbonyl, methoxyethylcarbonyl, methoxypropylcarbonyl, ethoxymethylcarbonyl, ethoxyethylcarbonyl, ethoxypropylcarbonyl, propoxymethylcarbonyl, propoxyethylcarbonyl, propoxypropylcarbonyl, methoxyphenylcarbonyl, ethoxyphenylcarbonyl, propoxyphenylcarbonyl, piperidinylmethylcarbonyl, piperazinylmethylcarbonyl, morpholinylcarbonyl, methylsulfonyl, ethylsulfonyl, methylsulfonylmethylene, amino, aminomethyl, aminoethyl, aminopropyl, N-methylamino, N,N-dimethylamino, N-ethylamino, N,N-diethylamino, N-propylamino, N,N-dipropylamino, phenylamino, benzylamino, methylaminomethylene, ethylaminomethylene, methylaminoethylene, ethylaminoethylene, aminocarbonyl, methylcarbonylamino, ethylcarbonylamino, methylaminomethylcarbonyl, ethylaminomethylcarbonyl, methylcarbonylaminoethylene, ethylcarbonylaminoethylene, aminomethylcarbonylaminoethylene, methoxycarbonylamino, ethoxycarbonylamino, methoxymethylcarbonylamino, methoxyethylcarbonylamino, ethoxymethylcarbonylamino, ethoxyethylcarbonylamino, methoxycarbonylaminoethylene, ethoxycarbonylaminoethylene, methylimidocarbonyl, ethylimidocarbonyl, amidino, methylamidino, methylamidino, benzylamidino, guanidino, guanidinomethylene, guanidinoethylene, and methylsulfonylamino; and

$R^{202}$  and  $R^{203}$  are independently selected from hydrido, methyl, ethyl, propyl, butyl, phenyl and benzyl; and

y is 0, 1 or 2; and

R<sup>4</sup> is phenyl, wherein said phenyl is optionally substituted with one or more radicals independently selected from fluoro, chloro, methyl, ethyl, methoxy and  
5 ethoxy; and

R<sup>5</sup> is selected from hydrido, fluoro, chloro, bromo, hydroxy, methyl, ethyl, propyl, benzyl, cyano, carboxy, methoxy, methoxycarbonyl, aminocarbonyl, acetyl, methylamino, dimethylamino, 2-methylbutylamino,  
10 ethylamino, dimethylaminoethylamino, hydroxyethylamino, hydroxypropylamino, hydroxybutylamino, hydroxycyclopropylamino, hydroxycyclobutylamino, hydroxycyclopentylamino, hydroxycyclohexylamino, imidazolylamino, morpholinylethylamino, (1-ethyl-2-  
15 hydroxy)ethylamino, piperidinylamino, pyridinylmethylamino, phenylmethylpiperidinylamino, aminomethyl, cyclopropylamino, amino, hydroxy, ethoxycarbonylamino, methoxyphenylmethylamino, phenylmethylamino, fluorophenylmethylamino,  
20 fluorophenylethylamino, methylaminoethylamino, dimethylaminoethylamino, methylaminopropylamino, dimethylaminopropylamino, methylaminobutylamino, dimethylaminobutylamino, methylaminopentylamino, dimethylaminopentylamino, ethylaminoethylamino,  
25 diethylaminoethylamino, ethylaminopropylamino, diethylaminopropylamino, ethylaminobutylamino, diethylaminobutylamino, ethylaminopentylamino, methylaminocarbonyl, methylcarbonyl, and ethylcarbonyl;  
or  
30 a pharmaceutically-acceptable salt or tautomer thereof.

A subclass of compounds of particular interest consists of those compounds of Formula XA wherein:

35 R<sup>1</sup> is selected from hydrido, methyl, ethyl, hydroxyethyl and propargyl; and



$R^2$  is  $R^{200}$ -cyclohexyl- $R^{201}$  wherein:

$R^{200}$  is selected from:

-  $(CR^{202}R^{203})_y-$ ;

-  $NR^{202}-$ ;

5 -S-;

-O-;

or  $R^{200}$  represents a bond;

$R^{201}$  represents one or more radicals selected from the group consisting of hydrido, chloro, fluoro, bromo,  
10 hydroxy, carboxy, keto, methyl, ethyl, propyl, hydroxymethyl, hydroxyethyl, hydroxypropyl, (1-hydroxy-1,1-dimethyl)ethyl, chloromethyl, chloroethyl, chloropropyl, fluoromethyl, fluoroethyl, fluoropropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl,  
15 benzyl, piperidinyl, piperazinyl, morpholinyl, piperidinylmethylenes, piperazinylmethylenes, morpholinylmethylenes, methoxy, ethoxy, propoxy, methoxymethylene, methoxyethylene, methoxypropylene, ethoxyethylene, ethoxypropylene, propoxyethylene,  
20 propoxypropylene, methoxyphenylene, ethoxyphenylene, propoxyphenylene, methylcarbonyl, ethylcarbonyl, propylcarbonyl, cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, benzoyl, chlorobenzoyl, fluorobenzoyl, hydroxymethylcarbonyl, hydroxyethylcarbonyl, hydroxypropylcarbonyl,  
25 carboxymethylcarbonyl, carboxyethylcarbonyl, carboxypropylcarbonyl, methoxymethylcarbonyl, methoxyethylcarbonyl, methoxypropylcarbonyl, ethoxymethylcarbonyl, ethoxyethylcarbonyl, ethoxypropylcarbonyl, propoxymethylcarbonyl, propoxyethylcarbonyl, propoxypropylcarbonyl, methoxyphenylcarbonyl, ethoxyphenylcarbonyl, propoxyphenylcarbonyl, piperidinylmethylcarbonyl, piperazinylmethylcarbonyl, morpholinylcarbonyl,  
30 methylsulfonyl, ethylsulfonyl, methylsulfonylmethylene, amino, aminomethyl, aminoethyl, aminopropyl, N-

methyamino, N,N-dimethylamino, N-ethylamino, N,N-diethylamino, N-propylamino, N,N-dipropylamino, phenylamino, benzylamino, methylaminomethylene, ethylaminomethylene, methylaminoethylene, ethylaminoethylene, aminocarbonyl, methylcarbonylamino, ethylcarbonylamino, methylaminomethylcarbonyl, ethylaminomethylcarbonyl, methylcarbonylaminomethylene, ethylcarbonylaminomethylene, aminomethylcarbonylamino-carbonylmethylene, methoxycarbonylamino, ethoxycarbonylamino, methoxymethylcarbonylamino, methoxyethylcarbonylamino, ethoxymethylcarbonylamino, ethoxyethylcarbonylamino, methoxycarbonylaminomethylene, and ethoxycarbonylaminomethylene; and

$R^{202}$  and  $R^{203}$  are independently selected from hydrido, methyl, ethyl, phenyl and benzyl; and  
y is 0, 1 or 2; and

$R^4$  is phenyl, wherein said phenyl is optionally substituted with one or more radicals independently selected from fluoro, chloro, methyl, ethyl, methoxy and ethoxy; and

$R^5$  is selected from hydrido, fluoro, chloro, bromo, hydroxy, methyl, ethyl, cyano, carboxy, methoxy, methoxycarbonyl, aminocarbonyl, acetyl, methylamino, dimethylamino, ethylamino, dimethylaminoethylamino, hydroxyethylamino, hydroxypropylamino, hydroxybutylamino, hydroxycyclopropylamino, hydroxycyclobutylamino, hydroxycyclopentylamino, hydroxycyclohexylamino, (1-ethyl-2-hydroxy)ethylamino, aminomethyl, cyclopropylamino, amino, ethoxycarbonylamino, methoxyphenylmethylamino, phenylmethylamino, fluorophenylmethylamino, fluorophenylethylamino, methylaminoethylamino, dimethylaminoethylamino, methylaminopropylamino, dimethylaminopropylamino, methylaminobutylamino, dimethylaminobutylamino, methylaminopentylamino, dimethylaminopentylamino, ethylaminoethylamino, diethylaminoethylamino,

ethylaminopropylamino, diethylaminopropylamino,  
ethylaminobutylamino, diethylaminobutylamino,  
ethylaminopentylamino, methylaminocarbonyl,  
methylcarbonyl, and ethylcarbonyl; or

5       a pharmaceutically-acceptable salt or tautomer thereof.

A subclass of compounds of specific interest consists of those compounds of Formula XA wherein:

10        $R^1$  is hydrido; and

$R^2$  is  $R^{200}$ -cyclohexyl- $R^{201}$  wherein:

$R^{200}$  is selected from:

methylene;

- $NR^{202}$ -;

15       -S-;

-O-;

or  $R^{200}$  represents a bond;

$R^{201}$  represents one or more radicals selected from the group consisting of hydrido, amino, aminomethyl, aminoethyl, aminopropyl, N-methylamino, N,N-dimethylamino, N-ethylamino, N,N-diethylamino, N-propylamino, N,N-dipropylamino, phenylamino, benzylamino, methylaminomethylene, ethylaminomethylene, methylaminoethylene, ethylaminoethylene, aminocarbonyl, methylcarbonylamino, ethylcarbonylamino, methylaminomethylcarbonyl, ethylaminomethylcarbonyl, methylcarbonylaminomethylene, ethylcarbonylaminomethylene, aminomethylcarbonylaminocarbonylmethylene, methoxycarbonylamino, ethoxycarbonylamino, methoxymethylcarbonylamino, methoxyethylcarbonylamino, ethoxymethylcarbonylamino, ethoxyethylcarbonylamino, methoxycarbonylaminomethylene, and ethoxycarbonylaminomethylene; and

35        $R^{202}$  is selected from hydrido, methyl, phenyl and benzyl; and

R<sup>4</sup> is phenyl, wherein said phenyl is optionally substituted with one or more radicals independently selected from fluoro, chloro, methyl, and methoxy; and

R<sup>5</sup> is selected from hydrido, methylamino,  
5 dimethylamino, 2-methylbutylamino, ethylamino, dimethylaminoethylamino, hydroxypropylamino, hydroxyethylamino, hydroxypropylamino, hydroxybutylamino, hydroxycyclopropylamino, hydroxycyclobutylamino, hydroxycyclopentylamino, hydroxycyclohexylamino, (1-ethyl-2-hydroxy)ethylamino, aminomethyl,  
10 cyclopropylamino, amino, dimethylaminoethylamino, dimethylaminopropylamino, dimethylaminobutylamino, dimethylaminopentylamino, diethylaminoethylamino, diethylaminopropylamino, diethylaminobutylamino, and  
15 diethylaminopentylamino; or  
a pharmaceutically-acceptable salt or tautomer thereof.

A subclass of compounds of high interest consists of  
20 those compounds of Formula XA wherein:

R<sup>1</sup> is hydrido; and

R<sup>2</sup> is R<sup>200</sup>-cyclohexyl-R<sup>201</sup> wherein:

R<sup>200</sup> is selected from:

methylene;

25 -NR<sup>202</sup>-;

-S-;

-O-;

or R<sup>200</sup> represents a bond;

R<sup>201</sup> represents one or more radicals selected from  
30 the group consisting of amino, aminomethyl, N,N-dimethylamino, and N-isopropylamino; and

R<sup>202</sup> is selected from hydrido and methyl; and

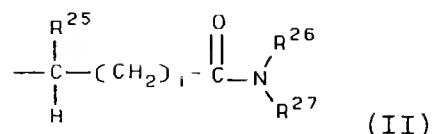
R<sup>4</sup> is phenyl, wherein said phenyl is optionally substituted with one or more radicals independently  
35 selected from fluoro, chloro, methyl, and methoxy; and

R<sup>5</sup> is selected from hydrido, hydroxypropylamino,

hydroxycyclohexylamino, and diethylaminoethylamino; or  
a pharmaceutically-acceptable salt or tautomer  
thereof.

5           Within Formula IA is another subclass of compounds  
of interest wherein:

          R<sup>1</sup> is selected from hydrido, hydroxy, alkyl,  
cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl,  
heterocyclyl, cycloalkylalkylene, cycloalkenylalkylene,  
10 heterocyclylalkylene, haloalkyl, haloalkenyl,  
haloalkynyl, hydroxyalkyl, hydroxyalkenyl,  
hydroxyalkynyl, aralkyl, aralkenyl, aralkynyl,  
arylheterocyclyl, carboxy, carboxyalkyl, alkoxyalkyl,  
alkenoxyalkyl, alkynoxyalkyl, aryloxyalkyl, alkoxyaryl,  
15 heterocyclyoxyalkyl, alkoxyalkoxy, mercaptoalkyl,  
alkylthioalkylene, alkenylthioalkylene,  
alkylthioalkenylene, amino, aminoalkyl, alkylamino,  
alkenylamino, alkynylamino, arylamino, heterocyclylamino,  
alkylsulfinyl, alkenylsulfinyl, alkynylsulfinyl,  
20 arylsulfinyl, heterocyclylsulfinyl, alkylsulfonyl,  
alkenylsulfonyl, alkynylsulfonyl, arylsulfonyl,  
heterocyclylsulfonyl, alkylaminoalkylene,  
alkylsulfonylalkylene, acyl, acyloxycarbonyl,  
alkoxycarbonylalkylene, aryloxycarbonylalkylene,  
25 heterocyclyoxyalkylene, alkoxycarbonylarylene,  
aryloxycarbonylarylene, heterocyclyoxyalkylene,  
alkylcarbonylalkylene, arylcarbonylalkylene,  
heterocyclylcarbonylalkylene, alkylcarbonylarylene,  
arylcarbonylarylene, heterocyclylcarbonylarylene,  
30 alkylcarbonyloxyalkylene, arylcarbonyloxyalkylene,  
heterocyclylcarbonyloxyalkylene, alkylcarbonyloxyarylene,  
arylcarbonyloxyarylene, and  
heterocyclylcarbonyloxyarylene; or  
          R<sup>1</sup> has the formula



wherein:

i is an integer from 0 to 9;

R<sup>25</sup> is selected from hydrogen, alkyl, aralkyl,  
 5 heterocyclylalkyl, alkoxyalkylene, aryloxyalkylene,  
 aminoalkyl, alkylaminoalkyl, arylaminoalkyl,  
 alkylcarbonylalkylene, arylcarbonylalkylene, and  
 heterocyclylcarbonylaminoalkylene; and

R<sup>26</sup> is selected from hydrogen, alkyl, alkenyl,  
 10 alkynyl, cycloalkylalkylene, aralkyl,  
 alkoxyalkylene, and alkylaminoalkyl; and

R<sup>27</sup> is selected from alkyl, cycloalkyl, alkynyl,  
 aryl, heterocyclyl, aralkyl, cycloalkylalkylene,  
 cycloalkenylalkylene, cycloalkylarylene,  
 15 cycloalkylcycloalkyl, heterocyclylalkylene, alkylarylene,  
 alkylaralkyl, aralkylarylene, alkylheterocyclyl,  
 alkylheterocyclylalkylene, alkylheterocyclylarylene,  
 aralkylheterocyclyl, alkoxyalkylene, alkoxyarylene,  
 alkoxyaralkyl, alkoxyheterocyclyl, alkoxyalkoxyarylene,  
 20 aryloxyarylene, aralkoxyarylene,  
 alkoxyheterocyclylalkylene, aryloxyalkoxyarylene,  
 alkoxyalkoxyarylene, alkoxyalkoxyheterocyclyl,  
 alkoxyalkoxyheterocyclylalkylene, aminoalkyl,  
 alkylaminoalkylene, arylaminocarbonylalkylene,  
 25 alkoxyarylaminocarbonylalkylene, aminocarbonylalkylene,  
 arylaminocarbonylalkylene, alkylaminocarbonylalkylene,  
 arylcarbonylalkylene, alkoxyalkoxyarylene,  
 aryloxyalkoxyarylene, alkylaryloxyalkoxyarylene,  
 arylcarbonylarylene, alkylarylcarbonylarylene,  
 30 alkoxyalkoxyheterocyclylarylene,  
 alkoxyalkoxyheterocyclylalkylene,  
 heterocyclylcarbonylalkylarylene, alkylthioalkylene,  
 cycloalkylthioalkylene, alkylthioarylene,

aralkylthioarylene, heterocyclylthioarylene,  
arylthioalkylarylene, arylsulfonylaminoalkylene,  
alkylsulfonylarylene, alkylaminosulfonylarylene; wherein  
said alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl,  
5 heterocyclylalkylene, alkylheterocyclylarylene,  
alkoxyarylene, aryloxyarylene, arylaminocarbonylalkylene,  
aryloxycarbonylarylene, arylcarbonylarylene,  
alkylthioarylene, heterocyclylthioarylene,  
arylthioalkylarylene, and alkylsulfonylarylene groups  
10 are optionally substituted with one or more radicals  
independently selected from alkyl, halo, haloalkyl,  
alkoxy, keto, amino, nitro, and cyano; or

$R^{27}$  is  $-\text{CHR}^{28}\text{R}^{29}$  wherein  $R^{28}$  is alkoxycarbonyl, and  $R^{29}$   
is selected from aralkyl, aralkoxyalkylene,  
15 heterocyclylalkylene, alkylheterocyclylalkylene,  
alkoxycarbonylalkylene, alkylthioalkylene, and  
aralkylthioalkylene; wherein said aralkyl and  
heterocyclyl groups are optionally substituted with one  
or more radicals independently selected from alkyl and  
20 nitro; or

$R^{26}$  and  $R^{27}$  together with the nitrogen atom to which  
they are attached form a heterocycle, wherein said  
heterocycle is optionally substituted with one or more  
radicals independently selected from alkyl, aryl,  
25 heterocyclyl, heterocyclylalkylene,  
alkylheterocyclylalkylene, aryloxyalkylene,  
alkoxyarylene, alkylaryloxyalkylene, alkylcarbonyl,  
alkoxycarbonyl, aralkoxycarbonyl, alkylamino and  
alkoxycarbonylamino; wherein said aryl,  
30 heterocyclylalkylene and aryloxyalkylene radicals are  
optionally substituted with one or more radicals  
independently selected from halogen, alkyl and alkoxy;  
and

$R^2$  is selected from mercapto,  
35 heterocyclylheterocyclyl, heterocyclylalkylheterocyclyl,  
N-alkyl-N-alkynyl-amino, aminocarbonylalkylene,

alkylcarbonylaminoalkylene,  
 aminoalkylcarbonylaminoalkylene,  
 alkylaminoalkylcarbonylamino, aminoalkylthio,  
 alkylaminocarbonylalkylthio,  
 5 alkylaminoalkylaminocarbonylalkylthio, cyanoalkylthio,  
 alkenylthio, alkynylthio, carboxyalkylthio,  
 alkoxy carbonylalkylthio, alkylsulfinyl, alkylsulfonyl,  
 alkoxy carbonylalkylamino, alkoxy carbonylaminoalkylene,  
 alkoxy carbonylaminoalkoxy, aralkylthio,  
 10 heterocyclylalkylthio, aminoalkoxy, cyanoalkoxy,  
 carboxyalkoxy, aryloxy, aralkoxy, alkenyloxy, alkynyloxy,  
 and heterocyclylalkyloxy; wherein the aryl, heterocyclyl,  
 heterocyclylalkyl, cycloalkyl and cycloalkenyl groups are  
 optionally substituted with one or more radicals  
 15 independently selected from halo, keto, amino, alkyl,  
 alkenyl, alkynyl, aryl, heterocyclyl, aralkyl,  
 heterocyclylalkyl, epoxyalkyl, amino(hydroxyalkyl)  
 carboxy, alkoxy, aryloxy, aralkoxy, haloalkyl,  
 alkylamino, alkynylamino, alkylaminoalkylamino,  
 20 heterocyclylalkylamino, alkylcarbonyl, alkoxy carbonyl,  
 alkylsulfonyl, arylsulfonyl, and aralkylsulfonyl; or

$R^2$  is  $R^{200}$ -heterocyclyl- $R^{201}$ ,  $R^{200}$ -aryl- $R^{201}$ , or  $R^{200}$ -  
 cycloalkyl- $R^{201}$  wherein:

$R^{200}$  is selected from:

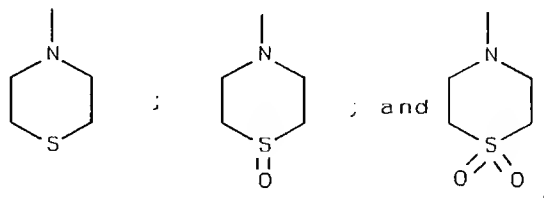
- 25 -  $(CR^{202}R^{203})_y-$ ;  
 -C(O)-;  
 -C(O)-(CH<sub>2</sub>)<sub>y</sub>-;  
 -C(O)-O-(CH<sub>2</sub>)<sub>y</sub>-;  
 - (CH<sub>2</sub>)<sub>y</sub>-C(O)-;  
 30 -O-(CH<sub>2</sub>)<sub>y</sub>-C(O)-;  
 -NR<sup>202</sup>-;  
 -NR<sup>202</sup>-(CH<sub>2</sub>)<sub>y</sub>-;  
 - (CH<sub>2</sub>)<sub>y</sub>-NR<sup>202</sup>-;  
 - (CH<sub>2</sub>)<sub>y</sub>-NR<sup>202</sup>-(CH<sub>2</sub>)<sub>z</sub>-;  
 35 - (CH<sub>2</sub>)<sub>y</sub>-C(O)-NR<sup>202</sup>-(CH<sub>2</sub>)<sub>z</sub>-;  
 - (CH<sub>2</sub>)<sub>y</sub>-NR<sup>202</sup>-C(O)-(CH<sub>2</sub>)<sub>z</sub>-;



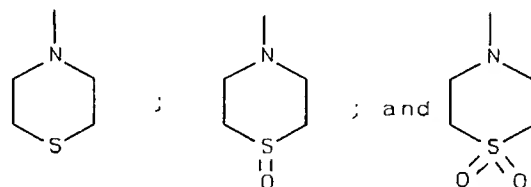
- $-(CH_2)_y-NR^{202}-C(O)-NR^{203}-(CH_2)_z-$ ;  
 $-S(O)_x-(CR^{202}R^{203})_y-$ ;  
 $-(CR^{202}R^{203})_y-S(O)_x-$ ;  
 $-S(O)_x-(CR^{202}R^{203})_y-O-$ ;  
5  $-S(O)_x-(CR^{202}R^{203})_y-C(O)-$ ;  
 $-O-(CH_2)_y-$ ;  
 $-(CH_2)_y-O-$ ;  
 $-S-$ ;  
 $-O-$ ;  
10 or  $R^{200}$  represents a bond;  
 $R^{201}$  represents one or more radicals selected from  
the group consisting of hydrido, halogen, hydroxy,  
carboxy, keto, alkyl, hydroxyalkyl, haloalkyl,  
cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl,  
15 aralkyl, heterocyclylalkylene, alkylcarbonyl,  
hydroxyalkylcarbonyl, cycloalkylcarbonyl, arylcarbonyl,  
haloarylcarbonyl, alkoxy, alkoxyalkylene, alkoxyarylene,  
alkoxycarbonyl, carboxyalkylcarbonyl,  
alkoxyalkylcarbonyl, heterocyclylalkylcarbonyl,  
20 alkylsulfonyl, alkylsulfonylalkylene, amino, aminoalkyl,  
alkylamino, aralkylamino, alkylaminoalkylene,  
aminocarbonyl, alkylcarbonylamino,  
alkylcarbonylaminoalkylene, alkylaminoalkylcarbonyl,  
alkylaminoalkylcarbonylamino,  
25 aminoalkylcarbonylaminoalkyl, alkoxycarbonylamino,  
alkoxyalkylcarbonylamino, alkoxycarbonylaminoalkylene,  
alkylimidocarbonyl, amidino, alkylamidino,  
aralkylamidino, guanidino, guanidinoalkylene, or  
alkylsulfonylamino; and  
30  $R^{202}$  and  $R^{203}$  are independently selected from hydrido,  
alkyl, aryl and aralkyl; and  
y and z are independently 0, 1, 2, 3, 4, 5 or 6  
wherein y + z is less than or equal to 6; and  
z is 0, 1 or 2; or  
35  $R^2$  is  $-NHCR^{204}R^{205}$  wherein  $R^{204}$  is alkylaminoalkylene,  
and  $R^{205}$  is aryl; or

$R^2$  is  $-C(NR^{206})R^{207}$  wherein  $R^{206}$  is selected from hydrogen and hydroxy, and  $R^{207}$  is selected from alkyl, aryl and aralkyl; and

$R^3$  is selected from pyridinyl, pyrimidinyl,  
 5 quinolinyl, purinyl, maleimidyl, pyridonyl, thiazolyl,  
 thiazolylalkyl, thiazolylamino,



wherein the  $R^3$  pyridinyl, pyrimidinyl, quinolinyl,  
 purinyl, maleimidyl, pyridonyl, thiazolyl,  
 10 thiazolylalkyl, thiazolylamino,



groups are optionally substituted with one or more radicals independently selected from halo, keto, alkyl, aralkyl, aralkenyl, arylheterocyclyl, carboxy,  
 15 carboxyalkyl, alkoxy, aryloxy, alkylthio, arylthio, alkylsulfinyl, arylsulfinyl, alkylsulfonyl, arylsulfonyl, aralkoxy, heterocyclylalkoxy, amino, alkylamino, alkenylamino, alkynylamino, cycloalkylamino, cycloalkenylamino, arylamino, haloaryl amino,  
 20 heterocyclylamino, aminocarbonyl, cyano, hydroxy, hydroxyalkyl, alkoxyalkylene, alkenoxyalkylene, aryloxyalkyl, alkoxyalkylamino, alkylaminoalkoxy, alkoxy carbonyl, aryloxy carbonyl, heterocyclyl oxy carbonyl, alkoxy carbonylamino, alkoxyaryl amino, alkoxyaralkyl amino,  
 25 aminosulfinyl, aminosulfonyl, alkylsulfonylamino,

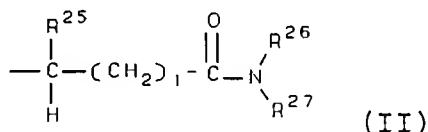
alkylaminoalkylamino, hydroxyalkylamino, aralkylamino,  
aryl(hydroxyalkyl)amino, alkylaminoalkylaminoalkylamino,  
alkylheterocyclylamino, heterocyclylalkylamino,  
alkylheterocyclylalkylamino, aralkylheterocyclylamino,  
5 heterocyclylheterocyclylalkylamino,  
alkoxycarbonylheterocyclylamino, nitro,  
alkylaminocarbonyl, alkylcarbonylamino, halosulfonyl,  
aminoalkyl, haloalkyl, alkylcarbonyl, hydrazinyl,  
alkylhydrazinyl, arylhydrazinyl, or  $-NR^{44}R^{45}$  wherein  $R^{44}$  is  
10 alkylcarbonyl or amino, and  $R^{45}$  is alkyl or aralkyl; and  
 $R^4$  is selected from hydrido, alkyl, alkenyl, alkynyl,  
cycloalkyl, cycloalkenyl, aryl, and heterocyclyl, wherein  
 $R^4$  is optionally substituted with one or more radicals  
independently selected from halo, alkyl, alkenyl,  
15 alkynyl, aryl, heterocyclyl, alkylthio, arylthio,  
alkylthioalkylene, arylthioalkylene, alkylsulfinyl,  
alkylsulfinylalkylene, arylsulfinylalkylene,  
alkylsulfonyl, alkylsulfonylalkylene,  
arylsulfonylalkylene, alkoxy, aryloxy, aralkoxy,  
20 aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl,  
alkoxycarbonyl, aryloxycarbonyl, haloalkyl, amino, cyano,  
nitro, alkylamino, arylamino, alkylaminoalkylene,  
arylaminoalkylene, aminoalkylamino, and hydroxy; or  
a pharmaceutically-acceptable salt or tautomer  
25 thereof.

Within Formula IA is another subclass of compounds  
of interest wherein:

$R^1$  is selected from hydrido, hydroxy, alkyl,  
30 cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl,  
heterocyclyl, cycloalkylalkylene, cycloalkenylalkylene,  
heterocyclylalkylene, haloalkyl, haloalkenyl,  
haloalkynyl, hydroxyalkyl, hydroxyalkenyl,  
hydroxyalkynyl, aralkyl, aralkenyl, aralkynyl,  
35 arylheterocyclyl, carboxy, carboxyalkyl, alkoxyalkyl,  
alkenoxyalkyl, alkynoxyalkyl, aryloxyalkyl, alkoxyaryl,

heterocyclyloxyalkyl, alkoxyalkoxy, mercaptoalkyl,  
 alkylthioalkylene, alkenylthioalkylene,  
 alkylthioalkenylene, amino, aminoalkyl, alkylamino,  
 alkenylamino, alkynylamino, arylamino, heterocyclylamino,  
 5 alkylsulfinyl, alkenylsulfinyl, alkynylsulfinyl,  
 arylsulfinyl, heterocyclylsulfinyl, alkylsulfonyl,  
 alkenylsulfonyl, alkynylsulfonyl, arylsulfonyl,  
 heterocyclylsulfonyl, alkylaminoalkylene,  
 alkylsulfonylalkylene, acyl, acyloxycarbonyl,  
 10 alkoxycarbonylalkylene, aryloxycarbonylalkylene,  
 heterocyclyloxycarbonylalkylene, alkoxycarbonylarylene,  
 aryloxycarbonylarylene, heterocyclyloxycarbonylarylene,  
 alkylcarbonylalkylene, arylcarbonylalkylene,  
 heterocyclylcarbonylalkylene, alkylcarbonylarylene,  
 15 arylcarbonylarylene, heterocyclylcarbonylarylene,  
 alkylcarbonyloxyalkylene, arylcarbonyloxyalkylene,  
 heterocyclylcarbonyloxyalkylene, alkylcarbonyloxyarylene,  
 arylcarbonyloxyarylene, and  
 heterocyclylcarbonyloxyarylene; or

20  $R^1$  has the formula



wherein:

i is an integer from 0 to 9;

25  $R^{25}$  is selected from hydrogen, alkyl, aralkyl,  
 heterocyclylalkyl, alkoxyalkylene, aryloxyalkylene,  
 aminoalkyl, alkylaminoalkyl, arylaminoalkyl,  
 alkylcarbonylalkylene, arylcarbonylalkylene, and  
 heterocyclylcarbonylaminoalkylene; and

30  $R^{26}$  is selected from hydrogen, alkyl, alkenyl,  
 alkynyl, cycloalkylalkylene, aralkyl,  
 alkoxycarbonylalkylene, and alkylaminoalkyl; and

$R^{27}$  is selected from alkyl, cycloalkyl, alkynyl,  
 aryl, heterocyclyl, aralkyl, cycloalkylalkylene,

cycloalkenylalkylene, cycloalkylarylene,  
 cycloalkylcycloalkyl, heterocyclylalkylene, alkylarylene,  
 alkylaralkyl, aralkylarylene, alkylheterocyclyl,  
 alkylheterocyclylalkylene, alkylheterocyclylarylene,  
 5 aralkylheterocyclyl, alkoxyalkylene, alkoxyarylene,  
 alkoxyaralkyl, alkoxyheterocyclyl, alkoxyalkoxyarylene,  
 aryloxyarylene, aralkoxyarylene,  
 alkoxyheterocyclylalkylene, aryloxyalkoxyarylene,  
 alkoxycarbonylalkylene, alkoxycarbonylheterocyclyl,  
 10 alkoxycarbonylheterocyclylcarbonylalkylene, aminoalkyl,  
 alkylaminoalkylene, arylaminocarbonylalkylene,  
 alkoxyarylaminocarbonylalkylene, aminocarbonylalkylene,  
 arylaminocarbonylalkylene, alkylaminocarbonylalkylene,  
 arylcarbonylalkylene, alkoxycarbonylarylene,  
 15 aryloxycarbonylarylene, alkylaryloxycarbonylarylene,  
 arylcarbonylarylene, alkylarylcarbonylarylene,  
 alkoxycarbonylheterocyclylarylene,  
 alkoxycarbonylalkoxylarylene,  
 heterocyclylcarbonylalkylarylene, alkylthioalkylene,  
 20 cycloalkylthioalkylene, alkylthioarylene,  
 aralkylthioarylene, heterocyclylthioarylene,  
 arylthioalkylarylene, arylsulfonylaminoalkylene,  
 alkylsulfonylarylene, alkylaminosulfonylarylene; wherein  
 said alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl,  
 25 heterocyclylalkylene, alkylheterocyclylarylene,  
 alkoxyarylene, aryloxyarylene, arylaminocarbonylalkylene,  
 aryloxycarbonylarylene, arylcarbonylarylene,  
 alkylthioarylene, heterocyclylthioarylene,  
 arylthioalkylarylene, and alkylsulfonylarylene groups  
 30 are optionally substituted with one or more radicals  
 independently selected from alkyl, halo, haloalkyl,  
 alkoxy, keto, amino, nitro, and cyano; or  
 $R^{27}$  is  $-CHR^{28}R^{29}$  wherein  $R^{28}$  is alkoxycarbonyl, and  $R^{29}$   
 is selected from aralkyl, aralkoxyalkylene,  
 35 heterocyclylalkylene, alkylheterocyclylalkylene,  
 alkoxycarbonylalkylene, alkylthioalkylene, and

aralkylthioalkylene; wherein said aralkyl and heterocyclcyl groups are optionally substituted with one or more radicals independently selected from alkyl and nitro; or

5         $R^{26}$  and  $R^{27}$  together with the nitrogen atom to which they are attached form a heterocycle, wherein said heterocycle is optionally substituted with one or more radicals independently selected from alkyl, aryl, heterocyclcyl, heterocyclcylalkylene,  
10 alkylheterocyclcylalkylene, aryloxyalkylene, alkoxyarylene, alkylaryloxyalkylene, alkylcarbonyl, alkoxycarbonyl, aralkoxycarbonyl, alkylamino and alkoxycarbonylamino; wherein said aryl, heterocyclcylalkylene and aryloxyalkylene radicals are  
15 optionally substituted with one or more radicals independently selected from halogen, alkyl and alkoxy; and

$R^2$  is selected from hydrido, halogen, mercapto, alkyl, alkenyl, alkynyl, aryl, heterocyclcyl, haloalkyl,  
20 hydroxyalkyl, aralkyl, alkylheterocyclcyl, heterocyclcylalkyl, heterocyclcylheterocyclcyl, heterocyclcylalkylheterocyclcyl, alkylamino, alkenylamino, alkynylamino, arylamino, aryl(hydroxyalkyl)amino, heterocyclcylamino, heterocyclcylalkylamino, aralkylamino,  
25 N-alkyl-N-alkynyl-amino, aminoalkyl, aminoaryl, aminoalkylamino, aminocarbonylalkylene, arylaminoalkylene, alkylaminoalkylene, arylaminoarylene, alkylaminoarylene, alkylaminoalkylamino, alkylcarbonylaminoalkylene,  
30 aminoalkylcarbonylaminoalkylene, alkylaminoalkylcarbonylamino, cycloalkyl, cycloalkenyl, aminoalkylthio, alkylaminocarbonylalkylthio, alkylaminoalkylaminocarbonylalkylthio, alkoxy, heterocyclcylloxy, alkylthio, cyanoalkylthio, alkenylthio,  
35 alkynylthio, carboxyalkylthio, arylthio, heterocyclcylthio, alkoxycarbonylalkylthio, alkylsulfinyl,

alkylsulfonyl, carboxy, carboxyalkyl, alkoxyalkyl,  
 alkoxyalkylthio, carboxycycloalkyl, carboxycycloalkenyl,  
 carboxyalkylamino, alkoxycarbonyl, heterocyclylcarbonyl,  
 alkoxycarbonylalkyl, alkoxycarbonylalkylamino,  
 5 alkoxycarbonylheterocyclyl,  
 alkoxycarbonylheterocyclylcarbonyl, alkoxyalkylamino,  
 alkoxycarbonylaminoalkylene, alkoxycarbonylaminoalkoxy,  
 alkoxycarbonylaminoalkylamino, heterocyclylsulfonyl,  
 aralkylthio, heterocyclylalkylthio, aminoalkoxy,  
 10 cyanoalkoxy, carboxyalkoxy, aryloxy, aralkoxy,  
 alkenyloxy, alkynyloxy, and heterocyclylalkyloxy; wherein  
 the aryl, heterocyclyl, heterocyclylalkyl, cycloalkyl and  
 cycloalkenyl groups are optionally substituted with one  
 or more radicals independently selected from halo, keto,  
 15 amino, alkyl, alkenyl, alkynyl, aryl, heterocyclyl,  
 aralkyl, heterocyclylalkyl, epoxyalkyl,  
 amino(hydroxyalkyl) carboxy, alkoxy, aryloxy, aralkoxy,  
 haloalkyl, alkylamino, alkynylamino,  
 alkylaminoalkylamino, heterocyclylalkylamino,  
 20 alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl,  
 arylsulfonyl, and aralkylsulfonyl; or

$R^2$  is  $R^{200}$ -heterocyclyl- $R^{201}$ ,  $R^{200}$ -aryl- $R^{201}$ , or  $R^{200}$ -  
 cycloalkyl- $R^{201}$  wherein:

$R^{200}$  is selected from:

- 25 -  $(CR^{202}R^{203})_y-$ ;  
 -C(O)-;  
 -C(O)-(CH<sub>2</sub>)<sub>y</sub>-;  
 -C(O)-O-(CH<sub>2</sub>)<sub>y</sub>-;  
 - (CH<sub>2</sub>)<sub>y</sub>-C(O)-;  
 30 -O-(CH<sub>2</sub>)<sub>y</sub>-C(O)-;  
 -NR<sup>202</sup>-;  
 -NR<sup>202</sup>-(CH<sub>2</sub>)<sub>y</sub>-;  
 - (CH<sub>2</sub>)<sub>y</sub>-NR<sup>202</sup>-;  
 - (CH<sub>2</sub>)<sub>y</sub>-NR<sup>202</sup>-(CH<sub>2</sub>)<sub>z</sub>-;  
 35 - (CH<sub>2</sub>)<sub>y</sub>-C(O)-NR<sup>202</sup>-(CH<sub>2</sub>)<sub>z</sub>-;  
 - (CH<sub>2</sub>)<sub>y</sub>-NR<sup>202</sup>-C(O)-(CH<sub>2</sub>)<sub>z</sub>-;

$-(CH_2)_y-NR^{202}-C(O)-NR^{203}-(CH_2)_z-$ ;  
 $-S(O)_x-(CR^{202}R^{203})_y-$ ;  
 $-(CR^{202}R^{203})_y-S(O)_x-$ ;  
 $-S(O)_x-(CR^{202}R^{203})_y-O-$ ;  
5  $-S(O)_x-(CR^{202}R^{203})_y-C(O)-$ ;  
 $-O-(CH_2)_y-$ ;  
 $-(CH_2)_y-O-$ ;  
 $-S-$ ;  
 $-O-$ ;

10 or  $R^{200}$  represents a bond;

$R^{201}$  represents one or more radicals selected from  
 the group consisting of hydrido, halogen, hydroxy,  
 carboxy, keto, alkyl, hydroxyalkyl, haloalkyl,  
 cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl,  
 15 aralkyl, heterocyclylalkylene, alkylcarbonyl,  
 hydroxyalkylcarbonyl, cycloalkylcarbonyl, arylcarbonyl,  
 haloarylcarbonyl, alkoxy, alkoxyalkylene, alkoxyarylene,  
 alkoxycarbonyl, carboxyalkylcarbonyl,  
 alkoxyalkylcarbonyl, heterocyclylalkylcarbonyl,  
 20 alkylsulfonyl, alkylsulfonylalkylene, amino, aminoalkyl,  
 alkylamino, aralkylamino, alkylaminoalkylene,  
 aminocarbonyl, alkylcarbonylamino,  
 alkylcarbonylaminoalkylene, alkylaminoalkylcarbonyl,  
 alkylaminoalkylcarbonylamino,  
 25 aminoalkylcarbonylaminoalkyl, alkoxycarbonylamino,  
 alkoxyalkylcarbonylamino, alkoxycarbonylaminoalkylene,  
 alkylimidocarbonyl, amidino, alkylamidino,  
 aralkylamidino, guanidino, guanidinoalkylene, or  
 alkylsulfonylamino; and

30  $R^{202}$  and  $R^{203}$  are independently selected from hydrido,  
 alkyl, aryl and aralkyl; and

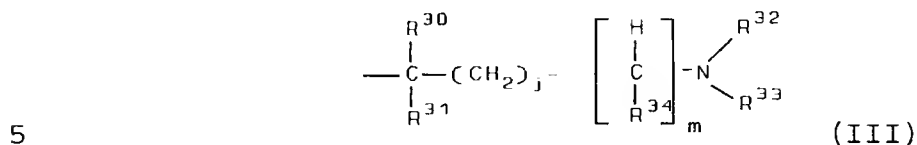
$y$  and  $z$  are independently 0, 1, 2, 3, 4, 5 or 6  
 wherein  $y + z$  is less than or equal to 6; and  
 $z$  is 0, 1 or 2; or

35  $R^2$  is  $-NHCR^{204}R^{205}$  wherein  $R^{204}$  is alkylaminoalkylene,  
 and  $R^{205}$  is aryl; or



$R^2$  is  $-C(NR^{206})R^{207}$  wherein  $R^{206}$  is selected from hydrogen and hydroxy, and  $R^{207}$  is selected from alkyl, aryl and aralkyl; or

$R^2$  has the formula:



wherein:

j is an integer from 0 to 8; and

m is 0 or 1; and

10  $R^{30}$  and  $R^{31}$  are independently selected from hydrogen, alkyl, aryl, heterocyclyl, aralkyl, heterocyclylalkylene, aminoalkyl, alkylaminoalkyl, aminocarbonylalkyl, alkoxyalkyl, and alkylcarbonyloxyalkyl; and

15  $R^{32}$  is selected from hydrogen, alkyl, aralkyl, heterocyclylalkyl, alkoxyalkylene, aryloxyalkylene, aminoalkyl, alkylaminoalkyl, arylaminoalkyl, alkylcarbonylalkylene, arylcarbonylalkylene, and heterocyclylcarbonylaminoalkylene;

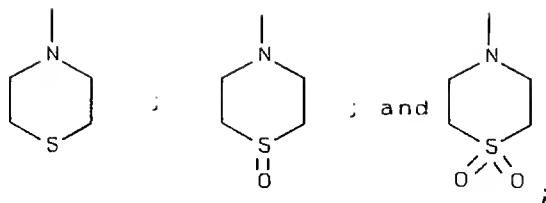
20  $R^{33}$  is selected from hydrogen, alkyl,  $-C(O)R^{35}$ ,  $-C(O)OR^{35}$ ,  $-SO_2R^{36}$ ,  $-C(O)NR^{37}R^{38}$ , and  $-SO_2NR^{39}R^{40}$ , wherein  $R^{35}$ ,  $R^{36}$ ,  $R^{37}$ ,  $R^{38}$ ,  $R^{39}$  and  $R^{40}$  are independently selected from hydrocarbon, heterosubstituted hydrocarbon and heterocyclyl; and

$R^{34}$  is selected from hydrogen, alkyl, aminocarbonyl, alkylaminocarbonyl, and arylaminocarbonyl; or

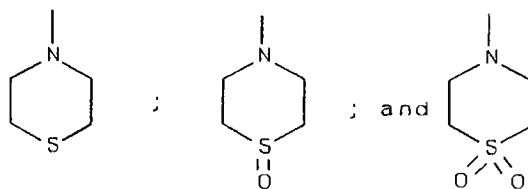
25  $R^2$  is  $-CR^{41}R^{42}$  wherein  $R^{41}$  is aryl, and  $R^{42}$  is hydroxy; and

$R^3$  is selected from pyridinyl, pyrimidinyl, quinolinyl, purinyl, maleimidyl, pyridonyl, thiazolyl, thiazolylalkyl, thiazolylamino,

131



wherein the R<sup>3</sup> pyridinyl, pyrimidinyl, quinolinyl, purinyl, maleimidyl, pyridonyl, thiazolyl, thiazolylalkyl, thiazolylamino,



5

groups are substituted with one or more radicals independently selected from keto, haloarylamino, alkoxyalkylene, alkenoxyalkylene, aryloxyalkyl, alkoxyalkylamino, alkylaminoalkoxy, alkoxyarylamino, alkylsulfonylamino, aryl(hydroxyalkyl)amino, alkylaminoalkylaminoalkylamino, alkylheterocyclylamino, alkylheterocyclylalkylamino, heterocyclylheterocyclylalkylamino, and alkoxycarbonylheterocyclylamino; and

R<sup>4</sup> is selected from hydrido, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, and heterocyclyl, wherein R<sup>4</sup> is optionally substituted with one or more radicals independently selected from halo, alkyl, alkenyl, alkynyl, aryl, heterocyclyl, alkylthio, arylthio, alkylthioalkylene, arylthioalkylene, alkylsulfinyl, alkylsulfinylalkylene, arylsulfinylalkylene, alkylsulfonyl, alkylsulfonylalkylene, arylsulfonylalkylene, alkoxy, aryloxy, aralkoxy, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkoxycarbonyl, aryloxy carbonyl, haloalkyl, amino, cyano,

nitro, alkylamino, arylamino, alkylaminoalkylene,  
arylaminoalkylene, aminoalkylamino, and hydroxy; or  
a pharmaceutically-acceptable salt or tautomer  
thereof.

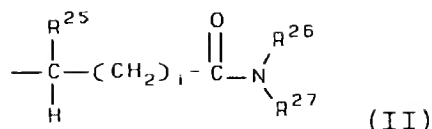
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Within Formula IA is another subclass of compounds  
of interest wherein:

R<sup>1</sup> is selected from hydrido, hydroxy, alkyl,  
cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl,  
10 heterocyclyl, cycloalkylalkylene, cycloalkenylalkylene,  
heterocyclalkylene, haloalkyl, haloalkenyl,  
haloalkynyl, hydroxyalkyl, hydroxyalkenyl,  
hydroxyalkynyl, aralkyl, aralkenyl, aralkynyl,  
arylheterocyclyl, carboxy, carboxyalkyl, alkoxyalkyl,  
15 alkenoxyalkyl, alkynoxyalkyl, aryloxyalkyl, alkoxyaryl,  
heterocyclalkoxy, mercaptoalkyl,  
alkylthioalkylene, alkenylthioalkylene,  
alkylthioalkenylene, amino, aminoalkyl, alkylamino,  
alkenylamino, alkynylamino, arylamino, heterocyclamino,  
20 alkylsulfinyl, alkenylsulfinyl, alkynylsulfinyl,  
arylsulfinyl, heterocyclsulfinyl, alkylsulfonyl,  
alkenylsulfonyl, alkynylsulfonyl, arylsulfonyl,  
heterocyclsulfonyl, alkylaminoalkylene,  
alkylsulfonylalkylene, acyl, acyloxycarbonyl,  
25 alkoxycarbonylalkylene, aryloxycarbonylalkylene,  
heterocyclalkoxy, alkoxycarbonylarylene,  
aryloxycarbonylarylene, heterocyclalkoxy, alkoxycarbonylarylene,  
alkylcarbonylalkylene, arylcarbonylalkylene,  
heterocyclcarbonylalkylene, alkylcarbonylarylene,  
30 arylcarbonylarylene, heterocyclcarbonylarylene,  
alkylcarbonyloxyalkylene, arylcarbonyloxyalkylene,  
heterocyclcarbonyloxyalkylene, alkylcarbonyloxyarylene,  
arylcarbonyloxyarylene, and  
heterocyclcarbonyloxyarylene; or

35

R<sup>1</sup> has the formula



wherein:

$i$  is an integer from 0 to 9;

$\text{R}^{25}$  is selected from hydrogen, alkyl, aralkyl,  
 5 heterocyclalkyl, alkoxyalkylene, aryloxyalkylene,  
 aminoalkyl, alkylaminoalkyl, arylaminoalkyl,  
 alkylcarbonylalkylene, arylcarbonylalkylene, and  
 heterocyclcarbonylaminoalkylene; and

$\text{R}^{26}$  is selected from hydrogen, alkyl, alkenyl,  
 10 alkynyl, cycloalkylalkylene, aralkyl,  
 alkoxycarbonylalkylene, and alkylaminoalkyl; and

$\text{R}^{27}$  is selected from alkyl, cycloalkyl, alkynyl,  
 aryl, heterocycl, aralkyl, cycloalkylalkylene,  
 cycloalkenylalkylene, cycloalkylarylene,  
 15 cycloalkylcycloalkyl, heterocyclalkylene, alkylarylene,  
 alkylaralkyl, aralkylarylene, alkylheterocycl,  
 alkylheterocyclalkylene, alkylheterocyclarylene,  
 aralkylheterocycl, alkoxyalkylene, alkoxyarylene,  
 alkoxyaralkyl, alkoxyheterocycl, alkoxyalkoxyarylene,  
 20 aryloxyarylene, aralkoxyarylene,  
 alkoxyheterocyclalkylene, aryloxyalkoxyarylene,  
 alkoxycarbonylalkylene, alkoxycarbonylheterocycl,  
 alkoxycarbonylheterocyclcarbonylalkylene, aminoalkyl,  
 alkylaminoalkylene, arylaminocarbonylalkylene,  
 25 alkoxyarylaminocarbonylalkylene, aminocarbonylalkylene,  
 arylaminocarbonylalkylene, alkylaminocarbonylalkylene,  
 arylcarbonylalkylene, alkoxycarbonylarylene,  
 aryloxycarbonylarylene, alkylaryloxycarbonylarylene,  
 arylcarbonylarylene, alkylarylcarbonylarylene,  
 30 alkoxycarbonylheterocyclarylene,  
 alkoxycarbonylalkoxyarylene,  
 heterocyclcarbonylalkylarylene, alkylthioalkylene,  
 cycloalkylthioalkylene, alkylthioarylene,

aralkylthioarylene, heterocyclylthioarylene,  
arylthioalkylarylene, arylsulfonylaminoalkylene,  
alkylsulfonylarylene, alkylaminosulfonylarylene; wherein  
said alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl,  
5 heterocyclylalkylene, alkylheterocyclylarylene,  
alkoxyarylene, aryloxyarylene, arylaminocarbonylalkylene,  
aryloxycarbonylarylene, arylcarbonylarylene,  
alkylthioarylene, heterocyclylthioarylene,  
arylthioalkylarylene, and alkylsulfonylarylene groups  
10 are optionally substituted with one or more radicals  
independently selected from alkyl, halo, haloalkyl,  
alkoxy, keto, amino, nitro, and cyano; or

$R^{27}$  is  $-CHR^{28}R^{29}$  wherein  $R^{28}$  is alkoxycarbonyl, and  $R^{29}$   
is selected from aralkyl, aralkoxyalkylene,  
15 heterocyclylalkylene, alkylheterocyclylalkylene,  
alkoxycarbonylalkylene, alkylthioalkylene, and  
aralkylthioalkylene; wherein said aralkyl and  
heterocyclyl groups are optionally substituted with one  
or more radicals independently selected from alkyl and  
20 nitro; or

$R^{26}$  and  $R^{27}$  together with the nitrogen atom to which  
they are attached form a heterocycle, wherein said  
heterocycle is optionally substituted with one or more  
radicals independently selected from alkyl, aryl,  
25 heterocyclyl, heterocyclylalkylene,  
alkylheterocyclylalkylene, aryloxyalkylene,  
alkoxyarylene, alkylaryloxyalkylene, alkylcarbonyl,  
alkoxycarbonyl, aralkoxycarbonyl, alkylamino and  
alkoxycarbonylamino; wherein said aryl,  
30 heterocyclylalkylene and aryloxyalkylene radicals are  
optionally substituted with one or more radicals  
independently selected from halogen, alkyl and alkoxy;  
and

$R^2$  is selected from hydrido, halogen, mercapto,  
35 alkyl, alkenyl, alkynyl, aryl, heterocyclyl, haloalkyl,  
hydroxyalkyl, aralkyl, alkylheterocyclyl,

heterocyclylalkyl, heterocyclylheterocyclyl,  
heterocyclylalkylheterocyclyl, alkylamino, alkenylamino,  
alkynylamino, arylamino, aryl(hydroxyalkyl)amino,  
heterocyclylamino, heterocyclylalkylamino, aralkylamino,  
5 N-alkyl-N-alkynyl-amino, aminoalkyl, aminoaryl,  
aminoalkylamino, aminocarbonylalkylene,  
arylaminoalkylene, alkylaminoalkylene, arylaminoarylene,  
alkylaminoarylene, alkylaminoalkylamino,  
alkylcarbonylaminoalkylene,  
10 aminoalkylcarbonylaminoalkylene,  
alkylaminoalkylcarbonylamino, cycloalkyl, cycloalkenyl,  
aminoalkylthio, alkylaminocarbonylalkylthio,  
alkylaminoalkylaminocarbonylalkylthio, alkoxy,  
heterocyclyloxy, alkylthio, cyanoalkylthio, alkenylthio,  
15 alkynylthio, carboxyalkylthio, arylthio,  
heterocyclylthio, alkoxycarbonylalkylthio, alkylsulfinyl,  
alkylsulfonyl, carboxy, carboxyalkyl, alkoxyalkyl,  
alkoxyalkylthio, carboxycycloalkyl, carboxycycloalkenyl,  
carboxyalkylamino, alkoxycarbonyl, heterocyclylcarbonyl,  
20 alkoxycarbonylalkyl, alkoxycarbonylalkylamino,  
alkoxycarbonylheterocyclyl,  
alkoxycarbonylheterocyclylcarbonyl, alkoxyalkylamino,  
alkoxycarbonylaminoalkylene, alkoxycarbonylaminoalkoxy,  
alkoxycarbonylaminoalkylamino, heterocyclylsulfonyl,  
25 aralkylthio, heterocyclylalkylthio, aminoalkoxy,  
cyanoalkoxy, carboxyalkoxy, aryloxy, aralkoxy,  
alkenylloxy, alkynylloxy, and heterocyclylalkyloxy; wherein  
the aryl, heterocyclyl, heterocyclylalkyl, cycloalkyl and  
cycloalkenyl groups are optionally substituted with one  
30 or more radicals independently selected from halo, keto,  
amino, alkyl, alkenyl, alkynyl, aryl, heterocyclyl,  
aralkyl, heterocyclylalkyl, epoxyalkyl,  
amino(hydroxyalkyl) carboxy, alkoxy, aryloxy, aralkoxy,  
haloalkyl, alkylamino, alkynylamino,  
35 alkylaminoalkylamino, heterocyclylalkylamino,  
alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl,

arylsulfonyl, and aralkylsulfonyl; or

$R^2$  is  $R^{200}$ -heterocyclyl- $R^{201}$ ,  $R^{200}$ -aryl- $R^{201}$ , or  $R^{200}$ -cycloalkyl- $R^{201}$  wherein:

$R^{200}$  is selected from:

- 5       -  $(CR^{202}R^{203})_y-$ ;
- $C(O)-$ ;
- $C(O)-(CH_2)_y-$ ;
- $C(O)-O-(CH_2)_y-$ ;
- $(CH_2)_y-C(O)-$ ;
- 10       -  $O-(CH_2)_y-C(O)-$ ;
- $NR^{202}-$ ;
- $NR^{202}-(CH_2)_y-$ ;
- $(CH_2)_y-NR^{202}-$ ;
- $(CH_2)_y-NR^{202}-(CH_2)_z-$ ;
- 15       -  $(CH_2)_y-C(O)-NR^{202}-(CH_2)_z-$ ;
- $(CH_2)_y-NR^{202}-C(O)-(CH_2)_z-$ ;
- $(CH_2)_y-NR^{202}-C(O)-NR^{203}-(CH_2)_z-$ ;
- $S(O)_x-(CR^{202}R^{203})_y-$ ;
- $(CR^{202}R^{203})_y-S(O)_x-$ ;
- 20       -  $S(O)_x-(CR^{202}R^{203})_y-O-$ ;
- $S(O)_x-(CR^{202}R^{203})_y-C(O)-$ ;
- $O-(CH_2)_y-$ ;
- $(CH_2)_y-O-$ ;
- $S-$ ;
- 25       -  $O-$ ;

or  $R^{200}$  represents a bond;

- $R^{201}$  represents one or more radicals selected from the group consisting of hydrido, halogen, hydroxy, carboxy, keto, alkyl, hydroxyalkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl, aralkyl, heterocyclylalkylene, alkylcarbonyl, hydroxyalkylcarbonyl, cycloalkylcarbonyl, arylcarbonyl, haloarylcarbonyl, alkoxy, alkoxyalkylene, alkoxyarylene, alkoxycarbonyl, carboxyalkylcarbonyl, alkoxyalkylcarbonyl, heterocyclylalkylcarbonyl, alkylsulfonyl, alkylsulfonylalkylene, amino, aminoalkyl,

alkylamino, aralkylamino, alkylaminoalkylene,  
 aminocarbonyl, alkylcarbonylamino,  
 alkylcarbonylaminoalkylene, alkylaminoalkylcarbonyl,  
 alkylaminoalkylcarbonylamino,  
 5 aminoalkylcarbonylaminoalkyl, alkoxy carbonylamino,  
 alkoxyalkylcarbonylamino, alkoxy carbonylaminoalkylene,  
 alkylimidocarbonyl, amidino, alkylamidino,  
 aralkylamidino, guanidino, guanidinoalkylene, or  
 alkylsulfonylamino; and

10  $R^{202}$  and  $R^{203}$  are independently selected from hydrido,  
 alkyl, aryl and aralkyl; and

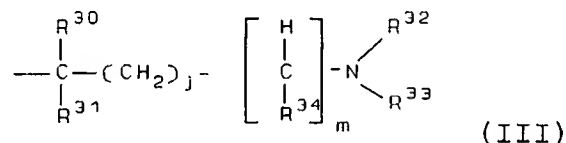
y and z are independently 0, 1, 2, 3, 4, 5 or 6  
 wherein y + z is less than or equal to 6; and

z is 0, 1 or 2; or

15  $R^2$  is  $-NHCR^{204}R^{205}$  wherein  $R^{204}$  is alkylaminoalkylene,  
 and  $R^{205}$  is aryl; or

$R^2$  is  $-C(NR^{206})R^{207}$  wherein  $R^{206}$  is selected from  
 hydrogen and hydroxy, and  $R^{207}$  is selected from alkyl,  
 aryl and aralkyl; or

20  $R^2$  has the formula:



wherein:

j is an integer from 0 to 8; and

m is 0 or 1; and

25  $R^{30}$  and  $R^{31}$  are independently selected from hydrogen,  
 Alkyl, aryl, heterocyclyl, aralkyl, heterocyclylalkylene,  
 aminoalkyl, alkylaminoalkyl, aminocarbonylalkyl,  
 alkoxyalkyl, and alkylcarbonyloxyalkyl; and

$R^{32}$  is selected from hydrogen, alkyl, aralkyl,  
 30 heterocyclylalkyl, alkoxyalkylene, aryloxyalkylene,  
 aminoalkyl, alkylaminoalkyl, arylaminoalkyl,  
 alkylcarbonylalkylene, arylcarbonylalkylene, and



heterocyclylcarbonylaminoalkylene;

$R^{33}$  is selected from hydrogen, alkyl,  $-C(O)R^{35}$ ,  
 $-C(O)OR^{35}$ ,  $-SO_2R^{36}$ ,  $-C(O)NR^{37}R^{38}$ , and  $-SO_2NR^{39}R^{40}$ , wherein  
 $R^{35}$ ,  $R^{36}$ ,  $R^{37}$ ,  $R^{38}$ ,  $R^{39}$  and  $R^{40}$  are independently

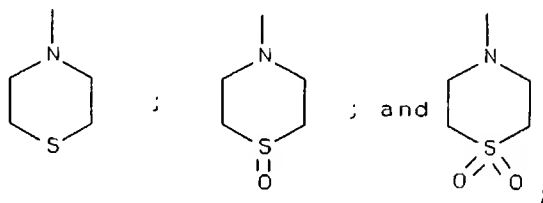
5 selected from hydrocarbon, heterosubstituted hydrocarbon  
 and heterocyclyl; and

$R^{34}$  is selected from hydrogen, alkyl, aminocarbonyl,  
 alkylaminocarbonyl, and arylaminocarbonyl; or

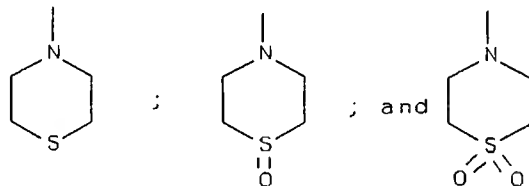
$R^2$  is  $-CR^{41}R^{42}$  wherein  $R^{41}$  is aryl, and  $R^{42}$  is hydroxy;

10 and

$R^3$  is selected from maleimidyl, pyridonyl, thiazolyl,  
 thiazolylalkyl, thiazolylamino,

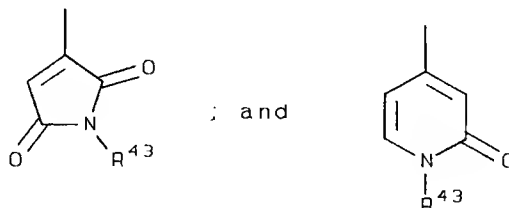


15 wherein the  $R^3$  maleimidyl, pyridonyl, thiazolyl,  
 thiazolylalkyl, thiazolylamino,



groups are optionally substituted with one or more  
 radicals independently selected from halo, keto, alkyl,  
 aralkyl, aralkenyl, arylheterocyclyl, carboxy,  
 20 carboxyalkyl, alkoxy, aryloxy, alkylthio, arylthio,  
 alkylsulfinyl, arylsulfinyl, alkylsulfonyl, arylsulfonyl,  
 aralkoxy, heterocyclylalkoxy, amino, alkylamino,  
 alkenylamino, alkynylamino, cycloalkylamino,  
 cycloalkenylamino, arylamino, haloaryl amino,  
 25 heterocyclylamino, aminocarbonyl, cyano, hydroxy,

hydroxyalkyl, alkoxyalkylene, alkenoxyalkylene,  
 aryloxyalkyl, alkoxyalkylamino, alkylaminoalkoxy,  
 alkoxycarbonyl, aryloxycarbonyl, heterocyclyloxycarbonyl,  
 alkoxycarbonylamino, alkoxyarylamino, alkoxyaralkylamino,  
 5 aminosulfinyl, aminosulfonyl, alkylsulfonylamino,  
 alkylaminoalkylamino, hydroxyalkylamino, aralkylamino,  
 aryl(hydroxyalkyl)amino, alkylaminoalkylaminoalkylamino,  
 alkylheterocyclylamino, heterocyclylalkylamino,  
 alkylheterocyclylalkylamino, aralkylheterocyclylamino,  
 10 heterocyclylheterocyclylalkylamino,  
 alkoxycarbonylheterocyclylamino, nitro,  
 alkylaminocarbonyl, alkylcarbonylamino, halosulfonyl,  
 aminoalkyl, haloalkyl, alkylcarbonyl, hydrazinyl,  
 alkylhydrazinyl, arylhydrazinyl, or  $-NR^{44}R^{45}$  wherein  $R^{44}$  is  
 15 alkylcarbonyl or amino, and  $R^{45}$  is alkyl or aralkyl; and  
 $R^4$  is selected from hydrido, alkyl, alkenyl, alkynyl,  
 cycloalkyl, cycloalkenyl, aryl, and heterocyclyl, wherein  
 $R^4$  is optionally substituted with one or more radicals  
 independently selected from halo, alkyl, alkenyl,  
 20 alkynyl, aryl, heterocyclyl, alkylthio, arylthio,  
 alkylthioalkylene, arylthioalkylene, alkylsulfinyl,  
 alkylsulfinylalkylene, arylsulfinylalkylene,  
 alkylsulfonyl, alkylsulfonylalkylene,  
 arylsulfonylalkylene, alkoxy, aryloxy, aralkoxy,  
 25 aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl,  
 alkoxycarbonyl, aryloxycarbonyl, haloalkyl, amino, cyano,  
 nitro, alkylamino, arylamino, alkylaminoalkylene,  
 arylaminoalkylene, aminoalkylamino, and hydroxy;  
 provided that  $R^3$  is other than maleimidyl or  
 30 pyridonyl having the structures:



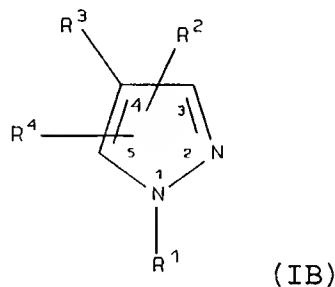
(IV)

(V)

respectively, wherein  $R^{43}$  is selected from hydrogen, alkyl, aminoalkyl, alkoxyalkyl, alkenoxyalkyl, and aryloxyalkyl; or

5 a pharmaceutically-acceptable salt or tautomer thereof.

Another group of compounds of interest consists of compounds of Formula IB:



wherein:

$R^1$  has the same definition as previously set forth in the description of compounds of Formula IA. In another embodiment,  $R^1$  is selected from hydrido, alkyl, hydroxyalkyl and alkynyl. In still another embodiment,  $R^1$  is hydrido;

$R^2$  is selected from at least one of the following four categories:

(1) piperidinyl substituted with one or more substituents selected from hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, alkoxyalkylene, alkoxyalkenylene, alkoxyalkynylene, and hydroxyacyl, wherein said hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, alkoxyalkylene, alkoxyalkenylene, alkoxyalkynylene, and hydroxyacyl substituents may be optionally substituted with one or more substituents selected from cycloalkyl, alkyl, aryl, arylalkyl, haloalkyl, and heteroarylalkyl, wherein

said cycloalkyl, alkyl, aryl, arylalkyl, haloalkyl, and heteroarylalkyl substituents may be optionally substituted with one or more substituents selected from alkylene, alkynylene, hydroxy, halo, haloalkyl, alkoxy, keto, amino, nitro, cyano, alkylsulfonyl, alkylsulfinyl, alkylthio, alkoxyalkyl, aryloxy, heterocyclyl, and heteroaralkoxy; or one or more substituents selected from hydroxycycloalkyl, alkoxycycloalkyl, and hydroxycycloalkylcarbonyl, wherein said hydroxycycloalkyl, alkoxycycloalkyl, and hydroxycycloalkylcarbonyl substituents may be optionally substituted with one or more substituents selected from cycloalkyl, alkyl, aryl, arylalkyl, haloalkyl, and heteroarylalkyl, wherein said cycloalkyl, alkyl, aryl, arylalkyl, haloalkyl, and heteroarylalkyl substituents may be optionally substituted with one or more substituents selected from alkylene, alkynylene, hydroxy, halo, haloalkyl, alkoxy, keto, amino, nitro, cyano, alkylsulfonyl, alkylsulfinyl, alkylthio, alkoxyalkyl, aryloxy, heterocyclyl, and heteroaralkoxy. In another embodiment, R<sup>2</sup> is piperidinyl substituted with one or more substituents selected from optionally substituted hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, alkoxyalkylene, alkoxyalkenylene, alkoxyalkynylene, hydroxyalkylcarbonyl, hydroxyalkenylcarbonyl, and hydroxyalkynylcarbonyl; or one or more substituents selected from optionally substituted hydroxycycloalkyl and hydroxycycloalkylcarbonyl. In still another embodiment, R<sup>2</sup> is piperidinyl substituted with one or more substituents selected from optionally substituted hydroxyalkyl, hydroxyalkenyl, alkoxyalkylene, alkoxyalkenylene, hydroxyalkylcarbonyl, and hydroxyalkenylcarbonyl, and hydroxycycloalkylcarbonyl. In still another

embodiment,  $R^2$  is piperidinyl substituted with at least one substituent selected from optionally substituted lower hydroxyalkyl, lower hydroxyalkylcarbonyl and hydroxycycloalkylcarbonyl.

5 In still another embodiment,  $R^2$  is piperidinyl substituted with 2-hydroxyacetyl, 2-hydroxypropionyl, 2-hydroxy-2-methylpropionyl, 2-hydroxy-2-phenylacetyl, 3-hydroxypropionyl, 2-hydroxy-3-methylbutyryl, 2-hydroxyisocapropropyl, 2-hydroxy-3-phenylpropionyl, 2-hydroxy-3-imidazolylpropionyl, 10 1-hydroxy-1-cyclohexylacetyl, 2-hydroxy-1-cyclohexylacetyl, 3-hydroxy-1-cyclohexylacetyl, 4-hydroxy-1-cyclohexylacetyl, 1-hydroxy-1-cyclopentylacetyl, 2-hydroxy-1-cyclopentylacetyl, 3-hydroxy-1-cyclopentylacetyl, 2-hydroxy-2-cyclohexylacetyl, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxyisopropyl, methoxymethylene, methoxyethylene, methoxypropylene, methoxyisopropylene, ethoxymethylene, 15 ethoxyethylene, ethoxypropylene, and ethoxyisopropylene. In each of the above embodiments, when  $R^2$  is piperidinyl, the piperidinyl ring may be substituted with at least one substituent attached to the distal nitrogen heteroatom or to a carbon ring atom adjacent to the distal nitrogen heteroatom of the piperidine ring. In each of the above embodiments, the piperidinyl ring may be monosubstituted at the distal nitrogen; and

30 (2) cyclohexyl substituted with one or more substituents selected from optionally substituted hydroxyalkyl, alkylaminoalkylene and cycloalkylamino. In another embodiment,  $R^2$  is cyclohexyl substituted with one or more substituents selected from optionally substituted lower hydroxyalkyl, lower alkylaminoalkylene and

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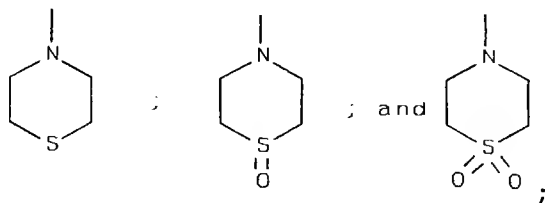
cycloalkylamino. In still another embodiment,  $R^2$  is cyclohexyl substituted with one or more substituents selected from optionally substituted lower hydroxyalkyl, lower dialkylaminoalkylene and cycloalkylamino. In still another embodiment,  $R^2$  is cyclohexyl substituted with one or more substituents selected from hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, methylaminomethylene, methylaminoethylene, methylaminopropylene, ethylaminomethylene, ethylaminoethylene, ethylaminopropylene, propylaminomethylene, propylaminoethylene, propylaminopropylene, dimethylaminomethylene, dimethylaminoethylene, dimethylaminopropylene, diethylaminomethylene, diethylaminoethylene, diethylaminopropylene, dipropylaminomethylene, dipropylaminoethylene, dipropylaminopropylene, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. In each of the above embodiments, when  $R^2$  is cyclohexyl, the cyclohexyl ring may be substituted with at least one substituent attached to the 4-position carbon atom of the cyclohexyl ring heteroatom of the piperidine ring. In each of the above embodiments, the cyclohexyl ring may be monosubstituted at the 4-position carbon atom; and

(3) cyclohexyl substituted with one or more optionally substituted alkylamino. In another embodiment,  $R^2$  is cyclohexyl substituted with optionally substituted lower alkylamino. In still another embodiment,  $R^2$  is cyclohexyl substituted with one or more substituents selected from optionally substituted methylamino, ethylamino, n-propylamino, isopropylamino, n-butylamino, sec-butylamino, t-butylamino, isobutylamino, dimethylamino, diethylamino, di-n-propylamino, di-isopropylamino, di-n-butylamino, di-sec-butylamino, di-t-butylamino,

and di-isobutylamino. In each of the above  
embodiments, when R<sup>2</sup> is cyclohexyl, the cyclohexyl  
ring may be substituted with at least one  
substituent attached to the 4-position carbon atom  
of the cyclohexyl ring heteroatom of the piperidine  
ring. In each of the above embodiments, the  
cyclohexyl ring may be monosubstituted at the 4-  
position carbon atom; and

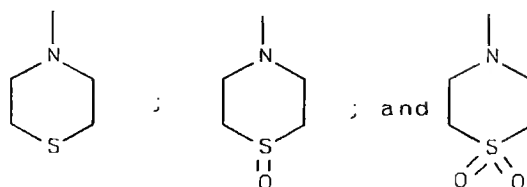
(4) piperidinylamino substituted with one or  
more alkynyl substituents. In another embodiment, R<sup>2</sup>  
is piperidinylamino substituted with optionally  
substituted lower alkynyl. In still another  
embodiment, R<sup>2</sup> is piperidinylamino substituted with  
optionally substituted ethynyl, propynyl and  
butynyl. In still another embodiment, R<sup>2</sup> is  
piperidinylamino substituted with optionally  
substituted propargyl. In still another embodiment,  
R<sup>2</sup> is 4-propargylpiperidinylamino. In each of the  
above embodiments, when R<sup>2</sup> is piperidinylamino, the  
piperidinyl ring may be substituted with at least  
one substituent attached to the distal nitrogen  
heteroatom or to a carbon ring atom adjacent to the  
distal nitrogen heteroatom of the piperidine ring.  
In each of the above embodiments, the piperidinyl  
ring may be monosubstituted at the distal nitrogen;  
and

R<sup>3</sup> is selected from pyridinyl, pyrimidinyl,  
quinolinyl, purinyl, maleimidyl, pyridonyl,  
thiazolyl, thiazolylalkyl, thiazolylamino,



wherein the R<sup>3</sup> pyridinyl, pyrimidinyl, quinolinyl,  
purinyl, maleimidyl, pyridonyl, thiazolyl,

thiazolylalkyl, thiazolylamino,



groups may be optionally substituted with one or  
 5 more substituents independently selected from  
 hydrogen, aryl, alkylamino, alkylthio, alkyloxy,  
 aryloxy, arylamino, arylthio, aralkoxy, wherein said  
 aryl, alkylamino, alkylthio, alkyloxy, aryloxy,  
 arylamino, arylthio, aralkoxy substituents may be  
 10 optionally substituted with one or more alkylene,  
 alkenylene, hydroxy, halo, haloalkyl, alkoxy, keto,  
 amino, nitro, cyano, alkylsulfonyl, alkylsulfinyl,  
 alkylthio, alkoxyalkyl, aryloxy, heterocyclyl, and  
 heteroaralkoxy. In another embodiment, R<sup>3</sup> is  
 15 optionally substituted pyridinyl or pyrimidinyl. In  
 still another embodiment, R<sup>3</sup> is unsubstituted  
 pyridinyl or pyrimidinyl; and

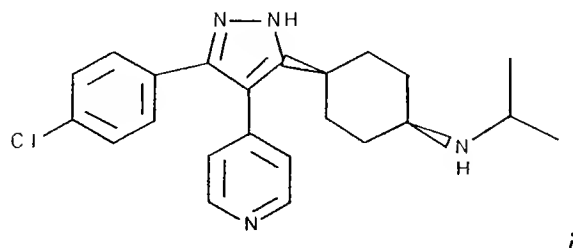
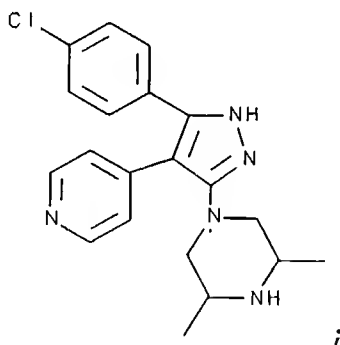
R<sup>4</sup> is selected from hydrido, alkyl, alkenyl,  
 alkynyl, cycloalkyl, cycloalkenyl, aryl, and  
 20 heterocyclyl, wherein R<sup>4</sup> is optionally substituted  
 with one or more substituents independently selected  
 from halo, haloalkyl, haloalkoxy, alkoxy, cyano,  
 hydroxy, alkyl, alkenyl, and alkynyl, wherein said  
 haloalkyl, haloalkoxy, alkoxy, cyano, hydroxy,  
 25 alkyl, alkenyl, and alkynyl substituents may be  
 optionally substituted with one or more alkylene,  
 alkenylene, alkynylene, hydroxy, halo, haloalkyl,  
 alkoxy, keto, amino, nitro, cyano, alkylsulfonyl,  
 alkylsulfinyl, alkylthio, alkoxyalkyl, aryloxy,  
 30 heterocyclyl, and heteroaralkoxy. In another  
 embodiment, R<sup>4</sup> is selected from optionally  
 substituted cycloalkyl, cycloalkenyl, aryl, and  
 heterocyclyl. In still another embodiment, R<sup>4</sup> is



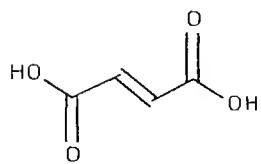
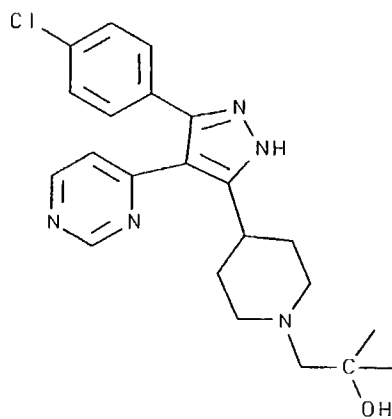
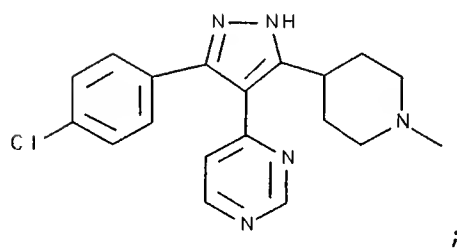
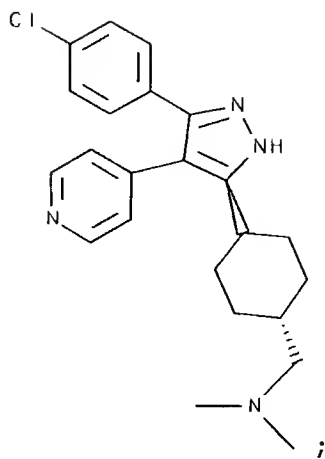
optionally substituted phenyl. In still another embodiment, R<sup>4</sup> is phenyl optionally substituted at a substitutable position with one or more radicals independently selected from chloro, fluoro, bromo and iodo. In still another embodiment, R<sup>4</sup> is phenyl optionally substituted at the meta or para position with one or more chloro radicals; or

a pharmaceutically-acceptable salt or tautomer thereof. Within each of the above embodiments, R<sup>2</sup> may be located at the 3-position of the pyrazole ring with R<sup>4</sup> located at the 5-position of the pyrazole ring. Alternatively, R<sup>2</sup> may be located at the 5-position of the pyrazole ring with R<sup>4</sup> located at the 3-position of the pyrazole ring.

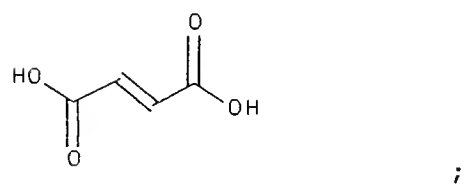
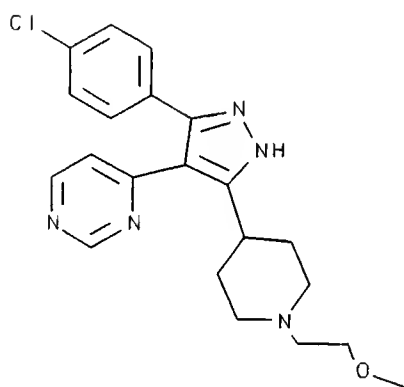
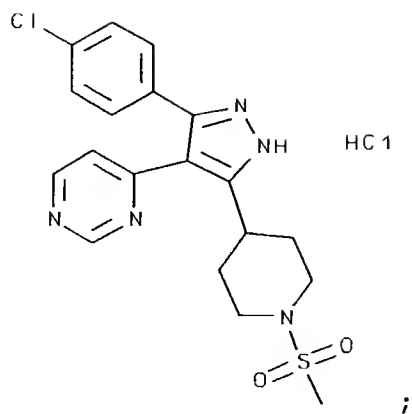
Still another group of compounds of interest consists of the compounds, their tautomers and their pharmaceutically acceptable salts, of the group consisting of:



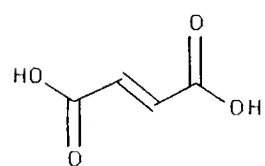
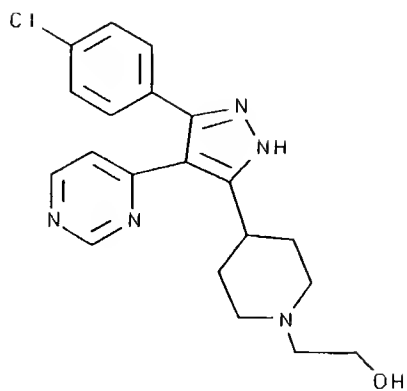
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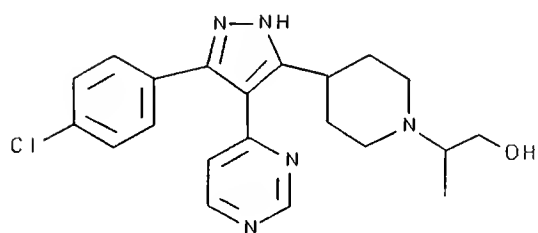
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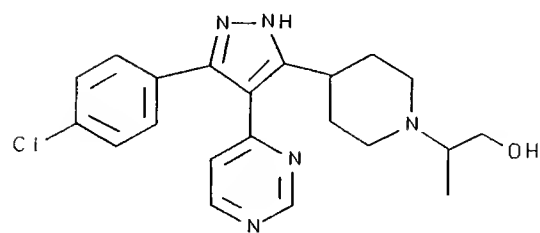
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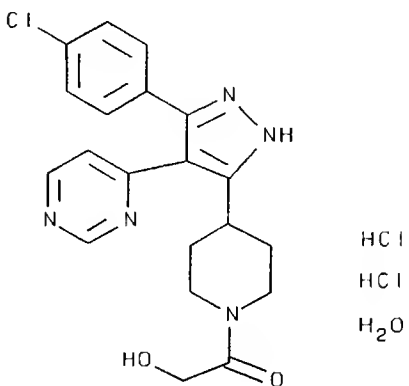
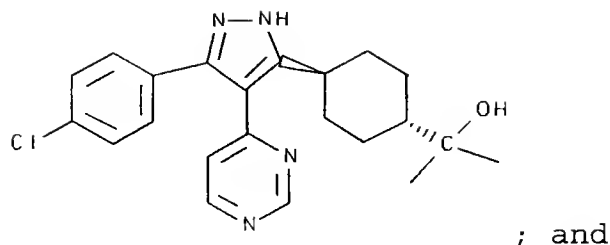


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The term "hydrido" denotes a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene (-CH<sub>2</sub>-) radical. Where used, either alone or within other terms such as "haloalkyl", "alkylsulfonyl", "alkoxyalkyl" and "hydroxyalkyl", "cyanoalkyl" and "mercaptoalkyl", the term "alkyl" embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl and the like. The term

"alkenyl" embraces linear or branched radicals having at least one carbon-carbon double bond of two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkenyl radicals are "lower alkenyl" radicals having two to about six carbon atoms. Examples of alkenyl radicals include ethenyl, allyl, propenyl, butenyl and 4-methylbutenyl. The terms "alkenyl" and "lower alkenyl", embrace radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations. The term "alkynyl" embraces linear or branched radicals having at least one carbon-carbon triple bond of two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkynyl radicals are "lower alkynyl" radicals having two to about six carbon atoms. Examples of alkynyl radicals include propargyl, 1-propynyl, 2-propynyl, 1-butyne, 2-butyne and 1-pentynyl. The term "cycloalkyl" embraces saturated carbocyclic radicals having three to about twelve carbon atoms. The term "cycloalkyl" embraces saturated carbocyclic radicals having three to about twelve carbon atoms. More preferred cycloalkyl radicals are "lower cycloalkyl" radicals having three to about eight carbon atoms. Examples of such radicals include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The term "cycloalkylalkylene" embraces alkyl radicals substituted with a cycloalkyl radical. More preferred cycloalkylalkylene radicals are "lower cycloalkylalkylene" which embrace lower alkyl radicals substituted with a lower cycloalkyl radical as defined above. Examples of such radicals include cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl and cyclohexylmethyl. The term "cycloalkenyl" embraces partially unsaturated carbocyclic radicals having three to twelve carbon atoms. Cycloalkenyl radicals that are partially unsaturated carbocyclic radicals that contain

two double bonds (that may or may not be conjugated) can be called "cycloalkyldienyl". More preferred cycloalkenyl radicals are "lower cycloalkenyl" radicals having four to about eight carbon atoms. Examples of such radicals include cyclobutenyl, cyclopentenyl and cyclohexenyl. The term "halo" means halogens such as fluorine, chlorine, bromine or iodine. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" embraces radicals having one to six carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl. The terms "alkoxy" and "alkyloxy" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and tert-butoxy.

The term "alkoxyalkyl" embraces alkyl radicals having one or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. The "alkoxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkoxy radicals. The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl. Aryl moieties may also be substituted at a substitutable position with one or more substituents selected independently from halo, alkyl, alkenyl, alkynyl, aryl, heterocyclyl, alkylthio, arylthio, alkylthioalkylene, arylthioalkylene, alkylsulfinyl, alkylsulfinylalkylene, arylsulfinylalkylene, alkylsulfonyl, alkylsulfonylalkylene, arylsulfonylalkylene, alkoxy, aryloxy, aralkoxy, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkoxycarbonyl, aryloxycarbonyl, haloalkyl, amino, cyano, nitro, alkylamino, arylamino, alkylaminoalkylene, arylaminoalkylene, aminoalkylamino, hydroxy, alkoxyalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkylene, acyl, carboxy, and aralkoxycarbonyl. The term "heterocyclyl" embraces saturated, partially unsaturated and unsaturated heteroatom-containing ring-shaped radicals, which can also be called "heterocyclyl", "heterocycloalkenyl" and "heteroaryl" correspondingly, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Examples of saturated heterocyclyl radicals include saturated 3 to 6-membered heteromonocyclic group containing 1 to 4 nitrogen atoms (e.g. pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and



1 to 3 nitrogen atoms (e.g. morpholinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., thiazolidinyl, etc.). Examples of partially unsaturated heterocyclyl radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole. Heterocyclyl radicals may include a pentavalent nitrogen, such as in tetrazolium and pyridinium radicals. The term "heteroaryl" embraces unsaturated heterocyclyl radicals. Examples of heteroaryl radicals include unsaturated 3 to 6 membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.) tetrazolyl (e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.; unsaturated condensed heterocyclyl group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl (e.g., tetrazolo[1,5-b]pyridazinyl, etc.), etc.; unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, furyl, etc.; unsaturated 3 to 6-membered heteromonocyclic group containing a sulfur atom, for example, thienyl, etc.; unsaturated 3- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.) etc.; unsaturated condensed heterocyclyl group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g. benzoxazolyl, benzoxadiazolyl, etc.); unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl (e.g., 1,2,4- thiadiazolyl, 1,3,4- thiadiazolyl, 1,2,5-thiadiazolyl, etc.) etc.; unsaturated

condensed heterocyclyl group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., benzothiazolyl, benzothiadiazolyl, etc.) and the like. The term "heterocycle" also embraces radicals where heterocyclyl radicals are fused with aryl or cycloalkyl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like. Said "heterocyclyl group" may have 1 to 3 substituents such as alkyl, hydroxyl, halo, alkoxy, oxo, amino, alkylthio and alkylamino. The term "heterocyclylalkylene" embraces heterocyclyl-substituted alkyl radicals. More preferred heterocyclylalkylene radicals are "lower heterocyclylalkylene" radicals having one to six carbon atoms and a heterocyclyl radicals. The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to about ten carbon atoms attached to a divalent sulfur atom. More preferred alkylthio radicals are "lower alkylthio" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthio radicals are methylthio, ethylthio, propylthio, butylthio and hexylthio. The term "alkylthioalkylene" embraces radicals containing an alkylthio radical attached through the divalent sulfur atom to an alkyl radical of one to about ten carbon atoms. More preferred alkylthioalkylene radicals are "lower alkylthioalkylene" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthioalkylene radicals include methylthiomethyl. The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to about ten carbon atoms, attached to a divalent  $-S(=O)-$  radical. More preferred alkylsulfinyl radicals are "lower alkylsulfinyl" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylsulfinyl radicals include methylsulfinyl, ethylsulfinyl, butylsulfinyl and hexylsulfinyl. The term "sulfonyl", whether used alone or linked to other terms

such as "alkylsulfonyl", "halosulfonyl" denotes a divalent radical,  $-\text{SO}_2-$ . "Alkylsulfonyl" embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. More preferred alkylsulfonyl radicals are "lower alkylsulfonyl" radicals having one to six carbon atoms. Examples of such lower alkylsulfonyl radicals include methylsulfonyl, ethylsulfonyl and propylsulfonyl. The "alkylsulfonyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkylsulfonyl radicals. The term "halosulfonyl" embraces halo radicals attached to a sulfonyl radical. Examples of such halosulfonyl radicals include chlorosulfonyl, and bromosulfonyl. The terms "sulfamyl", "aminosulfonyl" and "sulfonamidyl" denote  $\text{NH}_2\text{O}_2\text{S}-$ . The term "acyl" denotes a radical provided by the residue after removal of hydroxyl from an organic acid. Examples of such acyl radicals include alkanoyl and aroyl radicals. Examples of such alkanoyl radicals include formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, and radicals formed from succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, mandelic, pantothenic,  $\beta$ -hydroxybutyric, galactaric and galacturonic acids. The term "carbonyl", whether used alone or with other terms, such as "alkoxycarbonyl", denotes  $-(\text{C}=\text{O})-$ . The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes  $-\text{CO}_2\text{H}$ . The term "carboxyalkyl" embraces alkyl radicals substituted with a carboxy radical. More preferred are "lower carboxyalkyl" which embrace lower alkyl radicals as defined above, and may be additionally substituted on the alkyl radical with halo. Examples of such lower carboxyalkyl radicals include carboxymethyl, carboxyethyl and carboxypropyl. The term "alkoxycarbonyl" means a radical containing an alkoxy

radical, as defined above, attached via an oxygen atom to a carbonyl radical. More preferred are "lower alkoxy carbonyl" radicals with alkyl portions having one to six carbons. Examples of such lower alkoxy carbonyl (ester) radicals include substituted or unsubstituted methoxy carbonyl, ethoxy carbonyl, propoxy carbonyl, butoxy carbonyl and hexyloxy carbonyl. The term "alkoxy carbonyl alkyl" embraces alkyl radicals substituted with a alkoxy carbonyl radical as defined above. More preferred are "lower alkoxy carbonyl alkyl" radicals with alkyl portions having one to six carbons. Examples of such lower alkoxy carbonyl alkyl radicals include substituted or unsubstituted methoxy carbonyl methyl, ethoxy carbonyl methyl, methoxy carbonyl-ethyl and ethoxy carbonyl ethyl. The term "alkyl carbonyl", includes radicals having alkyl, hydroxyl alkyl, radicals, as defined herein, attached to a carbonyl radical. Examples of such radicals include substituted or unsubstituted methyl carbonyl, ethyl carbonyl, propyl carbonyl, butyl carbonyl, pentyl carbonyl, hydroxymethyl carbonyl, hydroxyethyl carbonyl. The term "aralkyl" embraces aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenylethyl, and diphenylethyl. The aryl in said aralkyl may be additionally substituted with one or more substituents selected independently from halo, alkyl, alkoxy, haloalkyl, haloalkoxy, amino and nitro. The terms benzyl and phenylmethyl are interchangeable. The term "heterocyclyl alkylene" embraces saturated and partially unsaturated heterocyclyl-substituted alkyl radicals (also can be called heterocycloalkyl alkylene and heterocycloalkenyl alkylene correspondingly), such as pyrrolidinylmethyl, and heteroaryl-substituted alkyl radicals (also can be called heteroaryl alkylene), such as pyridylmethyl, quinolylmethyl, thienylmethyl, furylethyl, and quinolylethyl. The heteroaryl in said heteroaralkyl

may be additionally substituted with halo, alkyl, alkoxy, haloalkyl and haloalkoxy. The term "aryloxy" embraces aryl radicals attached through an oxygen atom to other radicals. The term "aralkoxy" embraces aralkyl radicals attached through an oxygen atom to other radicals. The term "aminoalkyl" embraces alkyl radicals substituted with amino radicals. More preferred are "lower aminoalkyl" radicals. Examples of such radicals include aminomethyl, aminoethyl, and the like. The term "alkylamino" denotes amino groups which are substituted with one or two alkyl radicals. Preferred are "lower alkylamino" radicals having alkyl portions having one to six carbon atoms. Suitable lower alkylamino may be monosubstituted N-alkylamino or disubstituted N,N-alkylamino, such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino or the like. The term "arylamino" denotes amino groups which are substituted with one or two aryl radicals, such as N-phenylamino. The "arylamino" radicals may be further substituted on the aryl ring portion of the radical. The term "aminocarbonyl" denotes an amide group of the formula  $\text{C}(=\text{O})\text{NH}_2$ . The term "alkylaminocarbonyl" denotes an aminocarbonyl group which has been substituted with one or two alkyl radicals on the amino nitrogen atom. Preferred are "N-alkylaminocarbonyl" and "N,N-dialkylaminocarbonyl" radicals. More preferred are "lower N-alkylaminocarbonyl" and "lower N,N-dialkylaminocarbonyl" radicals with lower alkyl portions as defined above. The term "alkylcarbonylamino" embraces amino groups which are substituted with one alkylcarbonyl radicals. More preferred alkylcarbonylamino radicals are "lower alkylcarbonylamino" having lower alkylcarbonyl radicals as defined above attached to amino radicals. The term "alkylaminoalkylene" embraces radicals having one or more alkyl radicals attached to an aminoalkyl radical.

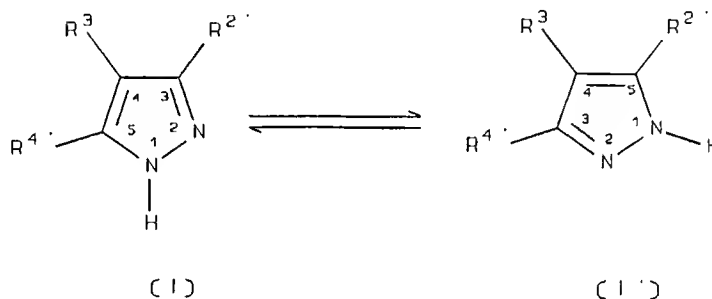
The "hydrocarbon" moieties described herein are organic compounds or radicals consisting exclusively of the elements carbon and hydrogen. These moieties include alkyl, alkenyl, alkynyl, and aryl moieties. These moieties also include alkyl, alkenyl, alkynyl, and aryl moieties substituted with other aliphatic or cyclic hydrocarbon groups, such as alkaryl, alkenaryl and alkynaryl. Preferably, these moieties comprise 1 to 20 carbon atoms.

The heterosubstituted hydrocarbon moieties described herein are hydrocarbon moieties which are substituted with at least one atom other than carbon, including moieties in which a carbon chain atom is substituted with a hetero atom such as nitrogen, oxygen, sulfur, or a halogen atom. These substituents include lower alkoxy such as methoxy, ethoxy, butoxy; halogen such as chloro or fluoro; ethers; acetals; ketals; esters; heterocyclyl such as furyl or thienyl; alkanoxy; hydroxy; protected hydroxy; acyl; acyloxy; nitro; cyano; amino; and amido.

The additional terms used to describe the substituents of the pyrazole ring and not specifically defined herein are defined in a similar manner to that illustrated in the above definitions. As above, more preferred substituents are those containing "lower" radicals. Unless otherwise defined to contrary, the term "lower" as used in this application means that each alkyl radical of a pyrazole ring substituent comprising one or more alkyl radicals has one to about six carbon atoms; each alkenyl radical of a pyrazole ring substituent comprising one or more alkenyl radicals has two to about six carbon atoms; each alkynyl radical of a pyrazole ring substituent comprising one or more alkynyl radicals has two to about six carbon atoms; each cycloalkyl or cycloalkenyl radical of a pyrazole ring substituent comprising one or more cycloalkyl and/or cycloalkenyl radicals is a 3 to 8 membered ring cycloalkyl or

cycloalkenyl radical, respectively; each aryl radical of a pyrazole ring substituent comprising one or more aryl radicals is a monocyclic aryl radical; and each heterocyclyl radical of a pyrazole ring substituent comprising one or more heterocyclyl radicals is a 4-8 membered ring heterocyclyl.

The present invention comprises the tautomeric forms of compounds of Formulae I and IX (as well as the compounds of Formulae (IA and IXA)). As illustrated below, the pyrazoles of Formula I and I' are magnetically and structurally equivalent because of the prototropic tautomeric nature of the hydrogen:



The present invention also comprises compounds of Formula I, IA, IX, IXA, X, XA and XI having one or more asymmetric carbons. It is known to those skilled in the art that those pyrazoles of the present invention having asymmetric carbon atoms may exist in diastereomeric, racemic, or optically active forms. All of these forms are contemplated within the scope of this invention. More specifically, the present invention includes enantiomers, diastereomers, racemic mixtures, and other mixtures thereof.

The present invention comprises a pharmaceutical composition for the treatment of a TNF mediated disorder, a p38 kinase mediated disorder, inflammation, and/or arthritis, comprising a therapeutically-effective amount

of a compound of Formula I and/or IA, or a therapeutically-acceptable salt or tautomer thereof, in association with at least one pharmaceutically-acceptable carrier, adjuvant or diluent.

The present invention further encompasses substituted pyrazoles that specifically bind to the ATP binding site of p38 kinase. Without being held to a particular theory, applicants hypothesize that these substituted pyrazoles interact with p38 kinase as set forth below. As the substituent at the 3-position of the pyrazole ring approaches the ATP binding site of p38 kinase, a hydrophobic cavity in the p38 kinase forms around the 3-position substituent at the binding site. This hydrophobic cavity is believed to form as the 3-position substituent binds to a specific peptide sequence of the enzyme. In particular, it is believed to bind to the sidechains of Lys<sub>52</sub>, Glu<sub>69</sub>, Leu<sub>73</sub>, Ile<sub>82</sub>, Leu<sub>84</sub>, Leu<sub>101</sub> and the methyl group of the Thr<sub>103</sub> sidechain of p38 kinase at the ATP binding site (wherein the numbering scheme corresponds to the numbering scheme conventionally used for ERK-2). Where the 3-position substituent is aryl or heteroaryl, such aryl or heteroaryl may be further substituted. It is hypothesized that such ring substituents may be beneficial in preventing hydroxylation or further metabolism of the ring.

The substituent at the 4-position of the pyrazole ring is one that is a partial mimic of the adenine ring of ATP, although it may be further elaborated. Preferably, it is a planar substituent terminated by a suitable hydrogen bond acceptor functionality. It is hypothesized that this acceptor hydrogen bonds to the backbone N-H of the Met<sub>106</sub> residue while one edge of this substituent is in contact with bulk solvent.

Substitution at the 5-position of the pyrazole ring is well tolerated and can provide increased potency and selectivity. It is hypothesized that such substituents

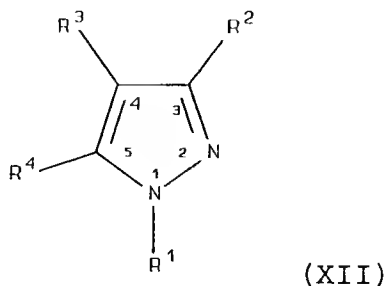


extend out in the direction of the bulk solvent and that suitable polar functionality placed at its terminus can interact with the sidechain of Asp<sup>109</sup>, leading to increased potency and selectivity.

Similarly, substitution on the nitrogen atom at the 1- or 2-position of the pyrazole ring is well tolerated and can provide increased potency. It is hypothesized that a hydrogen substituent attached to one of the ring nitrogen atoms is hydrogen bonded to Asp<sub>165</sub>. Preferably, the nitrogen atom at the 2-position is double bonded to the carbon atom at the 3-position of the pyrazole while the nitrogen atom at the 1-position of the pyrazole is available for substitution with hydrogen or other substituents.

The 5-position substituent and the 1- or 2-position substituent of the pyrazole can be selected so as to improve the physical characteristics, especially aqueous solubility and drug delivery performance, of the substituted pyrazole. Preferably, however, these substituents each have a molecular weight less than about 360 atomic mass units. More preferably, these substituents each have a molecular weight less than about less than about 250 atomic mass units. Still more preferably, these substituents have a combined molecular weight less than about 360 atomic mass units.

A class of substituted pyrazoles of particular interest consists of those compounds having the formula:



wherein

R<sup>1</sup> is a hydrocarbyl, heterosubstituted hydrocarbyl or heterocyclyl radical having a molecular weight less than about 360 atomic mass units; and

R<sup>2</sup> is a hydrocarbyl, heterosubstituted hydrocarbyl or heterocyclyl radical that binds with p38 kinase at said ATP binding site of p38 kinase; and

R<sup>3</sup> is a hydrocarbyl, heterosubstituted hydrocarbyl or heterocyclyl radical having a hydrogen bond acceptor functionality; and

R<sup>4</sup> is a hydrocarbyl, heterosubstituted hydrocarbyl or heterocyclyl radical having a molecular weight less than about 360 atomic mass units;

provided R<sup>3</sup> is not 2-pyridinyl when R<sup>4</sup> is a phenyl ring containing a 2-hydroxy substituent and when R<sup>1</sup> is hydrido; further provided R<sup>2</sup> is selected from aryl, heterocyclyl, unsubstituted cycloalkyl and cycloalkenyl when R<sup>4</sup> is hydrido; and further provided R<sup>4</sup> is not methylsulfonylphenyl; or

a pharmaceutically-acceptable salt or tautomer thereof.

In this embodiment of the invention, one or more of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> preferably are selected from the corresponding groups of the compounds of Formula I and/or IA. More preferably, R<sup>3</sup> is an optionally substituted pyridinyl or pyrimidinyl, R<sup>4</sup> is a halo substituted phenyl, and R<sup>1</sup> and R<sup>2</sup> have the definitions set forth immediately above.

A class of substituted pyrazoles of particular interest consists of those compounds of Formula XI wherein

R<sup>1</sup> is a hydrocarbyl, heterosubstituted hydrocarbyl or heterocyclyl radical having a molecular weight less than about 360 atomic mass units; and

R<sup>2</sup> is a hydrocarbyl, heterosubstituted hydrocarbyl or

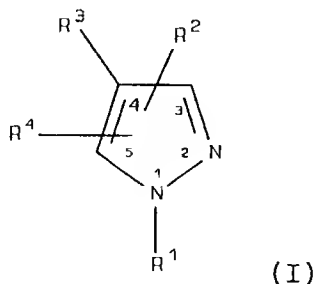
heterocyclyl radical wherein said radical binds with Lys<sub>52</sub>, Glu<sub>69</sub>, Leu<sub>73</sub>, Ile<sub>82</sub>, Leu<sub>84</sub>, Leu<sub>101</sub>, and Thr<sub>103</sub> sidechains at said ATP binding site of p38 kinase, said radical being substantially disposed within a hydrophobic cavity formed during said binding by p38 kinase at the ATP binding site; and

R<sup>3</sup> is a hydrocarbyl, heterosubstituted hydrocarbyl or heterocyclyl radical having a hydrogen bond acceptor functionality that hydrogen bonds with the N-H backbone of Met<sub>106</sub> of p38 kinase; and

R<sup>4</sup> is a hydrocarbyl, heterosubstituted hydrocarbyl or heterocyclyl radical having a molecular weight less than about 360 atomic mass units.

The present invention also comprises a therapeutic method of treating a TNF mediated disorder, a p38 kinase mediated disorder, inflammation and/or arthritis in a subject, the method comprising treating a subject having or susceptible to such disorder or condition with a therapeutically-effective amount of a compound of Formula I and/or IA.

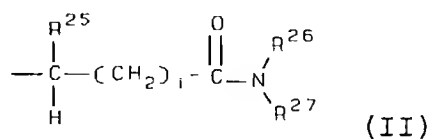
For example, in one embodiment the present invention comprises a therapeutic method of treating a TNF mediated disorder, a p38 kinase mediated disorder, inflammation and/or arthritis in a subject, the method comprising treating a subject having or susceptible to such disorder or condition with a therapeutically-effective amount of a compound of Formula I



wherein

R<sup>1</sup> is selected from hydrido, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heterocyclyl, cycloalkylalkylene, cycloalkenylalkylene, heterocyclylalkylene, haloalkyl, haloalkenyl, haloalkynyl, hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, aralkyl, aralkenyl, aralkynyl, arylheterocyclyl, carboxy, carboxyalkyl, alkoxyalkyl, alkenoxyalkyl, alkynoxyalkyl, aryloxyalkyl, heterocycliloxyalkyl, alkoxyalkoxy, mercaptoalkyl, alkylthioalkylene, alkenylthioalkylene, alkylthioalkenylene, amino, aminoalkyl, alkylamino, alkenylamino, alkynylamino, arylamino, heterocyclylamino, alkylsulfinyl, alkenylsulfinyl, alkynylsulfinyl, arylsulfinyl, heterocyclylsulfinyl, alkylsulfonyl, alkenylsulfonyl, alkynylsulfonyl, arylsulfonyl, heterocyclylsulfonyl, alkylaminoalkylene, alkylsulfonylalkylene, acyl, acyloxycarbonyl, alkoxycarbonylalkylene, aryloxycarbonylalkylene, heterocycliloxycarbonylalkylene, alkoxycarbonylarylene, aryloxycarbonylarylene, heterocycliloxycarbonylarylene, alkylcarbonylalkylene, arylcarbonylalkylene, heterocyclylcarbonylalkylene, alkylcarbonylarylene, arylcarbonylarylene, heterocyclylcarbonylarylene, alkylcarbonyloxyalkylene, arylcarbonyloxyalkylene, heterocyclylcarbonyloxyalkylene, alkylcarbonyloxyarylene, arylcarbonyloxyarylene, and heterocyclylcarbonyloxyarylene; or

R<sup>1</sup> has the formula



wherein:

i is an integer from 0 to 9;

R<sup>25</sup> is selected from hydrogen, alkyl, aralkyl,

heterocyclylalkyl, alkoxyalkylene, aryloxyalkylene, aminoalkyl, alkylaminoalkyl, arylaminoalkyl, alkylcarbonylalkylene, arylcarbonylalkylene, and heterocyclylcarbonylaminoalkylene; and

R<sup>26</sup> is selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkylalkylene, aralkyl, alkoxyalkylene, and alkylaminoalkyl; and

R<sup>27</sup> is selected from alkyl, cycloalkyl, alkynyl, aryl, heterocyclyl, aralkyl, cycloalkylalkylene, cycloalkenylalkylene, cycloalkylarylene, cycloalkylcycloalkyl, heterocyclylalkylene, alkylarylene, alkylaralkyl, aralkylarylene, alkylheterocyclyl, alkylheterocyclylalkylene, alkylheterocyclylarylene, aralkylheterocyclyl, alkoxyalkylene, alkoxyarylene, alkoxyaralkyl, alkoxyheterocyclyl, alkoxyalkoxyarylene, aryloxyarylene, aralkoxyarylene, alkoxyheterocyclylalkylene, aryloxyalkoxyarylene, alkoxyalkylene, alkoxyheterocyclyl, alkoxyalkylene, aminoalkyl, alkylaminoalkylene, arylaminocarbonylalkylene, alkoxyarylaminoalkylene, aminocarbonylalkylene, arylaminocarbonylalkylene, alkylaminocarbonylalkylene, arylcarbonylalkylene, alkoxyalkylene, aryloxyalkylene, alkylaryloxyalkylene, arylcarbonylalkylene, alkylaryloxyalkylene, alkoxyalkylene, heterocyclylalkylene, alkylthioalkylene, cycloalkylthioalkylene, alkylthioarylene, aralkylthioarylene, heterocyclylthioarylene, arylthioalkylene, arylsulfonylaminoalkylene, alkylsulfonylarylene, alkylaminosulfonylarylene; wherein said alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl, heterocyclylalkylene, alkylheterocyclylarylene, alkoxyarylene, aryloxyarylene, arylaminocarbonylalkylene, aryloxyalkylene, arylcarbonylalkylene,

alkylthioarylene, heterocyclylthioarylene, arylthioalkylarylene, and alkylsulfonylarylene groups are optionally substituted with one or more radicals independently selected from alkyl, halo, haloalkyl, alkoxy, keto, amino, nitro, and cyano; or

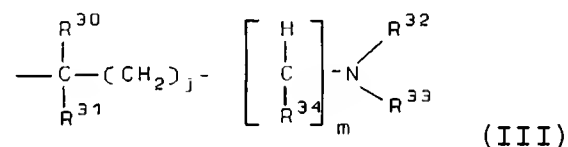
$R^{27}$  is  $-\text{CHR}^{28}\text{R}^{29}$  wherein  $R^{28}$  is alkoxycarbonyl, and  $R^{29}$  is selected from aralkyl, aralkoxyalkylene, heterocyclylalkylene, alkylheterocyclylalkylene, alkoxycarbonylalkylene, alkylthioalkylene, and aralkylthioalkylene; wherein said aralkyl and heterocyclyl groups are optionally substituted with one or more radicals independently selected from alkyl and nitro; or

$R^{26}$  and  $R^{27}$  together with the nitrogen atom to which they are attached form a heterocycle, wherein said heterocycle is optionally substituted with one or more radicals independently selected from alkyl, aryl, heterocyclyl, heterocyclylalkylene, alkylheterocyclylalkylene, aryloxyalkylene, alkoxyarylene, alkylaryloxyalkylene, alkylcarbonyl, alkoxycarbonyl, aralkoxycarbonyl, alkylamino and alkoxycarbonylamino; wherein said aryl, heterocyclylalkylene and aryloxyalkylene radicals are optionally substituted with one or more radicals independently selected from halogen, alkyl and alkoxy; and

$R^2$  is selected from hydrido, halogen, alkyl, alkenyl, alkynyl, aryl, heterocyclyl, haloalkyl, hydroxyalkyl, aralkyl, alkylheterocyclyl, heterocyclylalkyl, alkylamino, alkenylamino, alkynylamino, arylamino, heterocyclylamino, heterocyclylalkylamino, aralkylamino, aminoalkyl, aminoaryl, aminoalkylamino, arylaminoalkylene, alkylaminoalkylene, arylaminoarylene, alkylaminoarylene, alkylaminoalkylamino, cycloalkyl, cycloalkenyl, alkoxy, heterocycliloxy, alkylthio, arylthio, heterocyclylthio, carboxy, carboxyalkyl,

carboxycycloalkyl, carboxycycloalkenyl, carboxyalkylamino, alkoxycarbonyl, heterocyclylcarbonyl, alkoxycarbonylalkyl, alkoxycarbonylheterocyclyl, alkoxycarbonylheterocyclylcarbonyl, alkoxyalkylamino, alkoxycarbonylaminoalkylamino, and heterocyclylsulfonyl; wherein the aryl, heterocyclyl, heterocyclylalkyl, cycloalkyl and cycloalkenyl groups are optionally substituted with one or more radicals independently selected from halo, keto, amino, alkyl, alkenyl, alkynyl, aryl, heterocyclyl, aralkyl, heterocyclylalkyl, epoxyalkyl, amino(hydroxyalkyl) carboxy, alkoxy, aryloxy, aralkoxy, haloalkyl, alkylamino, alkynylamino, alkylaminoalkylamino, heterocyclylalkylamino, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, and aralkylsulfonyl; or

R<sup>2</sup> has the formula:



wherein:

j is an integer from 0 to 8; and

m is 0 or 1; and

R<sup>30</sup> and R<sup>31</sup> are independently selected from hydrogen, alkyl, aryl, heterocyclyl, aralkyl, heterocyclylalkylene, aminoalkyl, alkylaminoalkyl, aminocarbonylalkyl, alkoxyalkyl, and alkylcarbonyloxyalkyl; and

R<sup>32</sup> is selected from hydrogen, alkyl, aralkyl, heterocyclylalkyl, alkoxyalkylene, aryloxyalkylene, aminoalkyl, alkylaminoalkyl, arylaminoalkyl, alkylcarbonylalkylene, arylcarbonylalkylene, and heterocyclylcarbonylaminoalkylene;

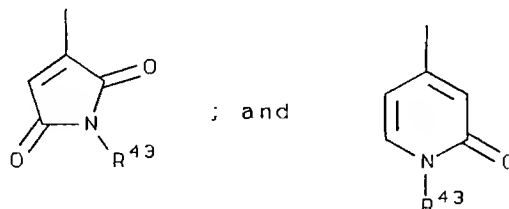
R<sup>33</sup> is selected from hydrogen, alkyl, -C(O)R<sup>35</sup>, -C(O)OR<sup>35</sup>, -SO<sub>2</sub>R<sup>36</sup>, -C(O)NR<sup>37</sup>R<sup>38</sup>, and -SO<sub>2</sub>NR<sup>39</sup>R<sup>40</sup>, wherein R<sup>35</sup>, R<sup>36</sup>, R<sup>37</sup>, R<sup>38</sup>, R<sup>39</sup> and R<sup>40</sup> are independently

selected from hydrocarbon, heterosubstituted hydrocarbon and heterocyclyl; and

$R^{34}$  is selected from hydrogen, alkyl, aminocarbonyl, alkylaminocarbonyl, and arylaminocarbonyl; or

$R^2$  is  $-CR^{41}R^{42}$  wherein  $R^{41}$  is aryl, and  $R^{42}$  is hydroxy; and

$R^3$  is selected from pyridinyl, pyrimidinyl, quinolinyl, purinyl,



(IV)

(V)

wherein  $R^{43}$  is selected from hydrogen, alkyl, aminoalkyl, alkoxyalkyl, alkenoxyalkyl, and aryloxyalkyl; and

wherein the  $R^3$  pyridinyl, pyrimidinyl, quinolinyl and purinyl groups are optionally substituted with one or more radicals independently selected from halo, alkyl, aralkyl, aralkenyl, arylheterocyclyl, carboxy, carboxyalkyl, alkoxy, aryloxy, alkylthio, arylthio, alkylsulfinyl, arylsulfinyl, alkylsulfonyl, arylsulfonyl, aralkoxy, heterocyclylalkoxy, amino, alkylamino, alkenylamino, alkynylamino, cycloalkylamino, cycloalkenylamino, arylamino, heterocyclylamino, aminocarbonyl, cyano, hydroxy, hydroxyalkyl, alkoxy carbonyl, aryloxy carbonyl, heterocyclyl oxy carbonyl, alkoxy carbonyl amino, alkoxy aralkyl amino, aminosulfinyl, aminosulfonyl, alkyl amino alkyl amino, hydroxy alkyl amino, aralkyl amino, heterocyclyl alkyl amino, aralkyl heterocyclyl amino, nitro, alkyl aminocarbonyl, alkyl carbonyl amino, halo sulfonyl, amino alkyl, halo alkyl, alkyl carbonyl, hydrazinyl, alkyl hydrazinyl,



arylhydrazinyl, or  $-NR^{44}R^{45}$  wherein  $R^{44}$  is alkylcarbonyl or amino, and  $R^{45}$  is alkyl or aralkyl; and

$R^4$  is selected from hydrido, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, and heterocyclyl, wherein  $R^4$  is optionally substituted with one or more radicals independently selected from halo, alkyl, alkenyl, alkynyl, aryl, heterocyclyl, alkylthio, arylthio, alkylthioalkylene, arylthioalkylene, alkylsulfinyl, alkylsulfinylalkylene, arylsulfinylalkylene, alkylsulfonyl, alkylsulfonylalkylene, arylsulfonylalkylene, alkoxy, aryloxy, aralkoxy, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkoxycarbonyl, aryloxycarbonyl, haloalkyl, amino, cyano, nitro, alkylamino, arylamino, alkylaminoalkylene, arylaminoalkylene, aminoalkylamino, and hydroxy;

provided  $R^3$  is not 2-pyridinyl when  $R^4$  is a phenyl ring containing a 2-hydroxy substituent and when  $R^1$  is hydrido; further provided  $R^2$  is selected from aryl, heterocyclyl, unsubstituted cycloalkyl and cycloalkenyl when  $R^4$  is hydrido; and further provided  $R^4$  is not methylsulfonylphenyl; or

a pharmaceutically-acceptable salt or tautomer thereof.

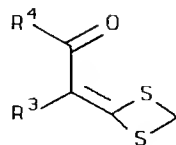
The present invention also is directed to the use of the compounds of Formula I and/or IA in the preparation of medicaments useful in the treatment and/or prophylaxis of p38 kinase mediated conditions and disorders.

Also included in the family of compounds of Formulae I and/or IA are the pharmaceutically-acceptable salts and prodrugs thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-

acceptable. Suitable pharmaceutically-acceptable acid addition salts of compounds of Formulae I and/or IA may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclyl, carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, stearic, salicylic, *p*-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, cyclohexylaminosulfonic, algenic,  $\beta$ -hydroxybutyric, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formula I and/or IA include metallic salts and organic salts. More preferred metallic salts include, but are not limited to appropriate alkali metal (group Ia) salts, alkaline earth metal (group IIa) salts and other physiological acceptable metals. Such salts can be made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc. Preferred organic salts can be made from tertiary amines and quaternary ammonium salts, including in part, tromethamine, diethylamine, *N,N'*-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (*N*-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound of Formulae I and/or IA by reacting, for example, the appropriate acid or base with the compound of Formulae I and/or IA.

The present invention additionally comprises a class

of compounds defined by Formula XX:



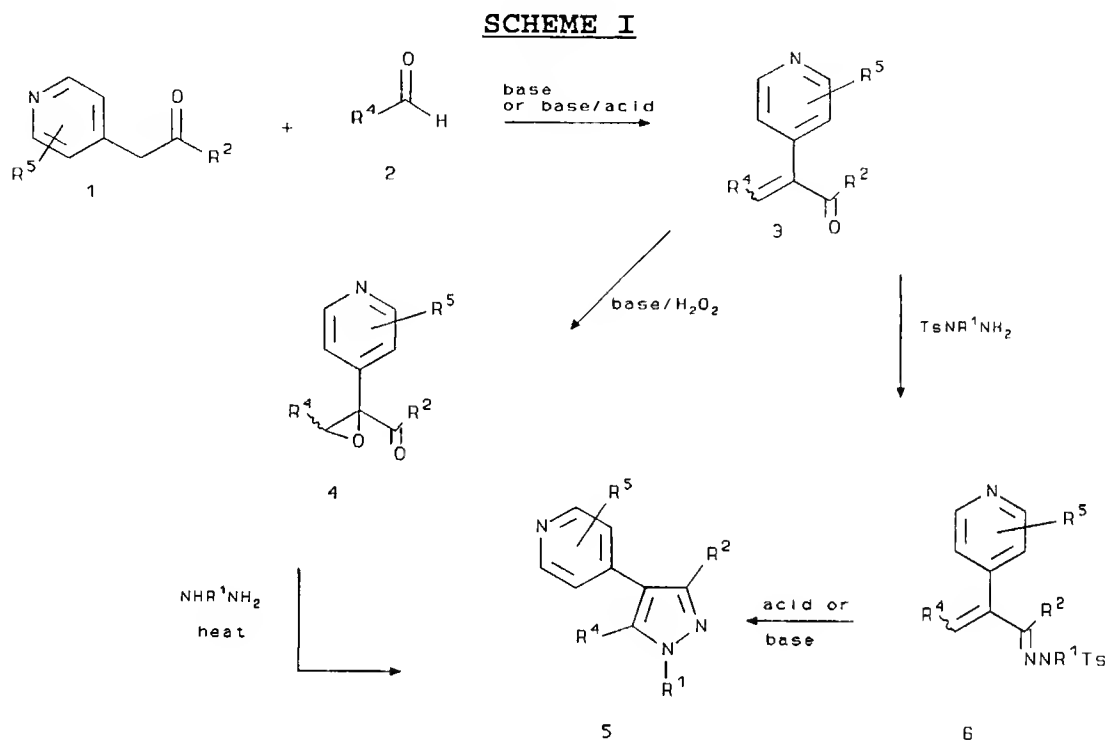
(XX)

wherein R<sup>3</sup> and R<sup>4</sup> are as defined for the compounds of Formulae I and/or IA. Also included in the family of compounds of Formula XX are the pharmaceutically-acceptable salts and prodrugs thereof.

The compounds of Formula XX are useful as intermediates in the preparation of the compounds of Formulae I and/or IA. In addition, the compounds of Formula XX themselves have been found to show usefulness as p38 kinase inhibitors. These compounds are useful for the prophylaxis and treatment of the same p38 kinase mediated disorders and conditions as the compounds of formulae I and/or IA. Accordingly, the present invention provides a method of treating a cytokine-mediated disease which comprises administering an effective cytokine-interfering amount of a compound of Formula XX or a pharmaceutically acceptable salt or prodrug thereof.

The present invention further comprises a pharmaceutical composition for the treatment of a TNF mediated disorder, a p38 kinase mediated disorder, inflammation, and/or arthritis, comprising a therapeutically-effective amount of a compound of Formula XX, or a therapeutically-acceptable salt or prodrug thereof, in association with at least one pharmaceutically-acceptable carrier, adjuvant or diluent.

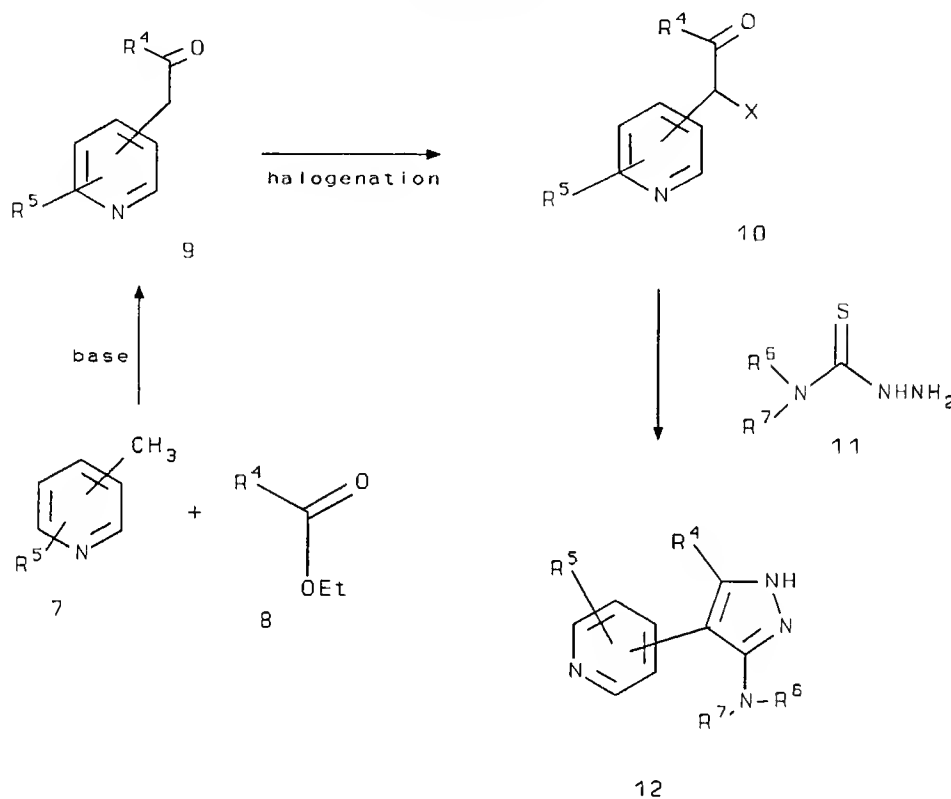
The compounds of the invention can be prepared according to the following procedures of Schemes I-XXIX wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$  and  $Ar^1$  are as previously defined for the compounds of Formula I, IX, X and XI except where expressly noted.



Scheme I shows the synthesis of pyrazole 5 by two routes. Condensation of the pyridylmethyl ketone 1 with aldehyde 2 in the presence of a base, such as piperidine, in a solvent, such as toluene or benzene, either in the absence or the presence of acetic acid at reflux, provides the  $\alpha,\beta$ -unsaturated ketone 3. In route 1, ketone 3 is first converted to epoxide 4, such as by treatment with hydrogen peroxide solution at room temperature, in the presence of base such as sodium hydroxide. Treatment of epoxide 4 with hydrazine in ethanol or other suitable solvent at a temperature ranging up to reflux, yields pyrazole 5. In route 2, ketone 3 is condensed directly with tosyl hydrazide in the presence of an acid such as acetic acid, at reflux,

to provide pyrazole 5. Alternatively, the intermediate tosyl hydrazone 6 may be isolated, conversion of it to pyrazole 5 is effected by treatment with a base, such as potassium hydroxide, in a suitable solvent, such as ethylene glycol, at a temperature ranging from 25 °C up to 150 °C.

**SCHEME II**



Scheme II shows the synthesis of pyrazole 12 of the present invention. The treatment of pyridine derivative 7 with ester 8 in the presence of a base, such as sodium bis(trimethylsilyl)amide, in a suitable solvent, such as tetrahydrofuran, gives ketone 9. Treatment of ketone 9 or a hydrohalide salt of ketone 9 with a halogenating agent, such as bromine, N-bromosuccinimide or N-chlorosuccinimide, in suitable solvents, such as acetic acid, methylene chloride, methanol, or combinations thereof, forms the α-halogenated ketone 10 (wherein X is halo). Examples of suitable hydrohalide salts include

the hydrochloride and hydrobromide salts. Reaction of haloketone 10 with thiosemicarbazide 11 (where R<sup>6</sup> and R<sup>7</sup> can be hydrido, lower alkyl, phenyl, heterocyclyl and the like or where R<sup>6</sup> and R<sup>7</sup> form a heterocyclyl ring optionally containing an additional heteroatom) provides pyrazole 12. Examples of suitable solvents for this reaction are ethanol and dimethylformamide. The reaction may be carried out in the presence or absence of base or acid at temperatures ranging from room temperature to 100 °C.

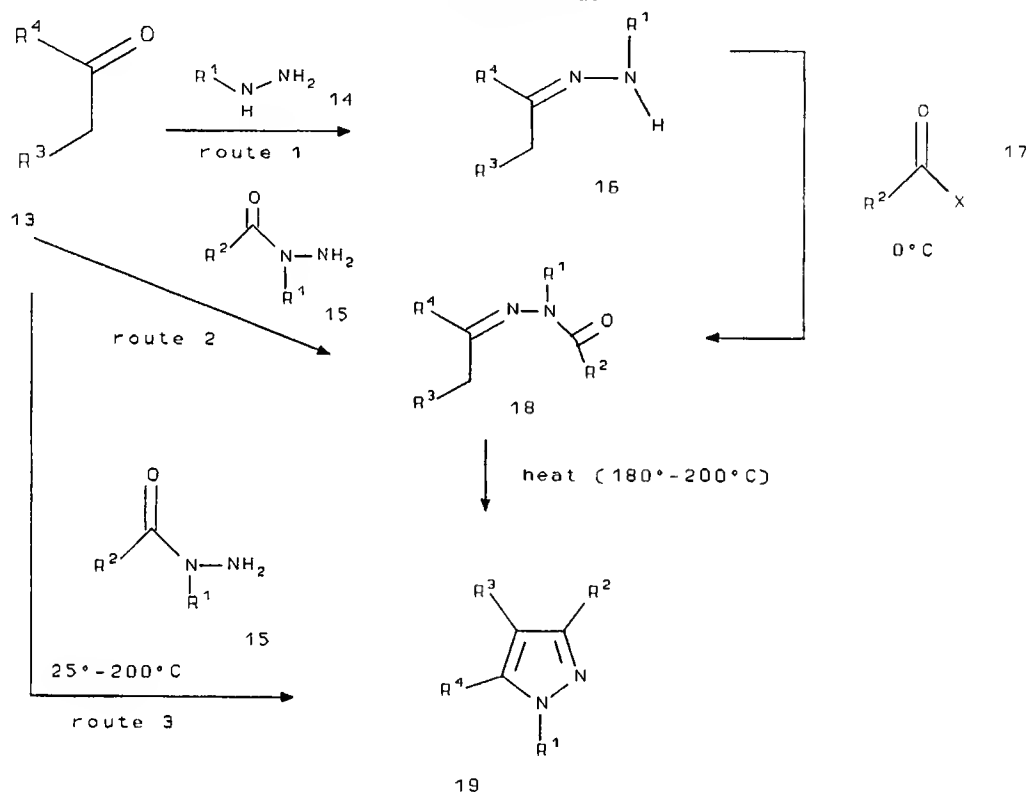
Thiosemicarbazides which are not commercially available may be conveniently prepared by one skilled in the art by first reacting an appropriate amine with carbon disulfide in the presence of a base, followed by treatment with an alkylating agent such as methyl iodide. Treatment of the resultant alkyl dithiocarbamate with hydrazine results in the desired thiosemicarbazide. This chemistry is further described in E. Lieber and R.C. Orlowski, J. Org. Chem., Vol. 22, p. 88 (1957). An alternative approach is to add hydrazine to appropriately substituted thiocyanates as described by Y. Nomoto et al., Chem. Pharm. Bull., Vol. 39, p.86 (1991). The Lieber and Nomoto publications are incorporated herein by reference.

Where Compound 12 contains a second derivatizable nitrogen atom, a wide range of substituents may be placed on that atom by methods known to those skilled in the art. For example, in cases where R<sup>6</sup> and R<sup>7</sup> together with the nitrogen atom to which they are attached comprise a piperazine ring, the distal nitrogen of that ring may be, for example, (i) methylated by reaction with formic acid and formaldehyde; (ii) propargylated by reaction with propargyl bromide in a suitable solvent such as dimethylformamide in the presence of a suitable base such as potassium carbonate; (iii) acylated or sulfonylated by reaction with a suitable acyl or sulfonyl derivative in

pyridine; or (iv) cyclopropanated by reaction with [1(1-ethoxycyclopropyl)oxy]trimethylsilane using sodium cyanoborohydride in the presence of acetic acid.

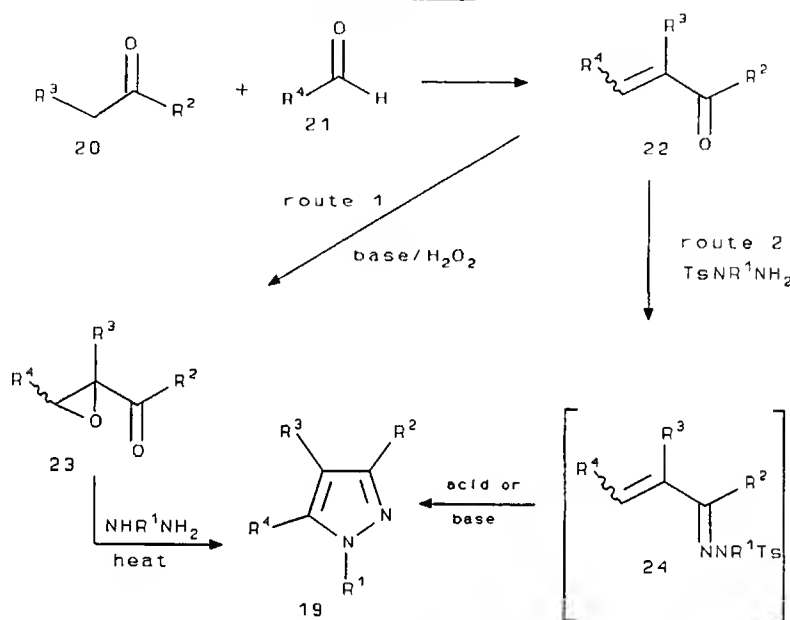
Additionally, one of the nitrogen atoms of the pyrazole ring optionally may be alkylated by reaction with an alkyl halide, such as propargyl bromide, in the presence of a strong base such as sodium hydride.

### SCHEME III



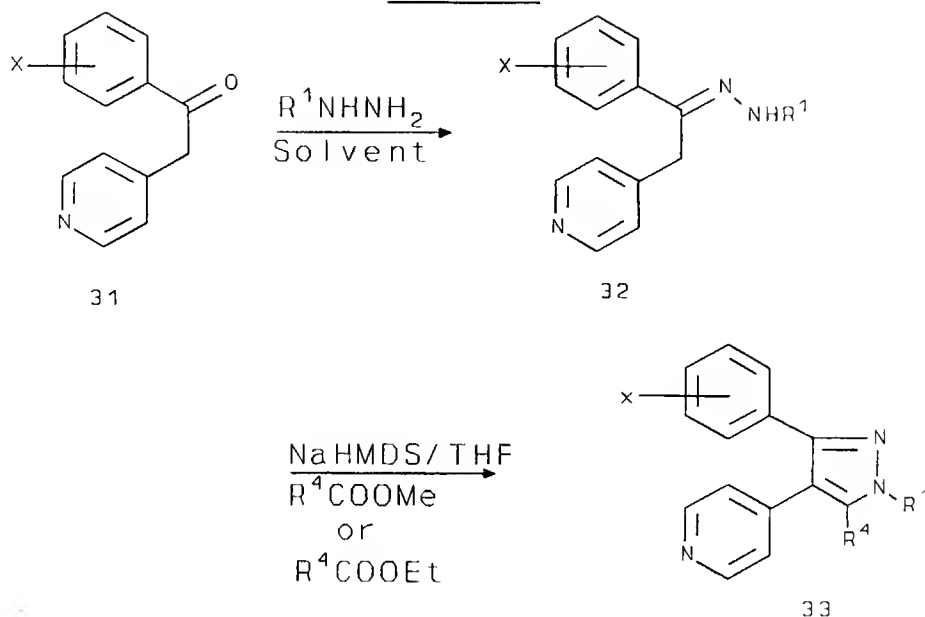
Scheme III shows the synthesis of pyrazole 19 in more general form by three routes. In Route 1, ketone 13 is condensed with hydrazine 14 to give the substituted hydrazone 16, which is then reacted with acyl halide or anhydride 17 at low temperature to provide acyl hydrazone 18. Upon heating at a temperature up to  $200^\circ C$ , acyl hydrazone 18 is converted to pyrazole 19. In Route 2, acyl hydrazone 18 is formed directly by reaction of ketone 13 with acyl hydrazone 15, formed by reaction of hydrazine with a carboxylic acid ester, at room

temperature. Heating acyl hydrazone **18** as above then provides pyrazole **19**. In Route 3, ketone **13** is treated with acyl hydrazide **15** at a suitable temperature, ranging from room temperature to about 200 °C, to give pyrazole **19** directly. Alternatively, this condensation may be carried out in an acidic solvent, such as acetic acid, or in a solvent containing acetic acid.

**SCHEME IV**

Synthetic Scheme IV describes the preparation of pyrazole **19**.



SCHEME V

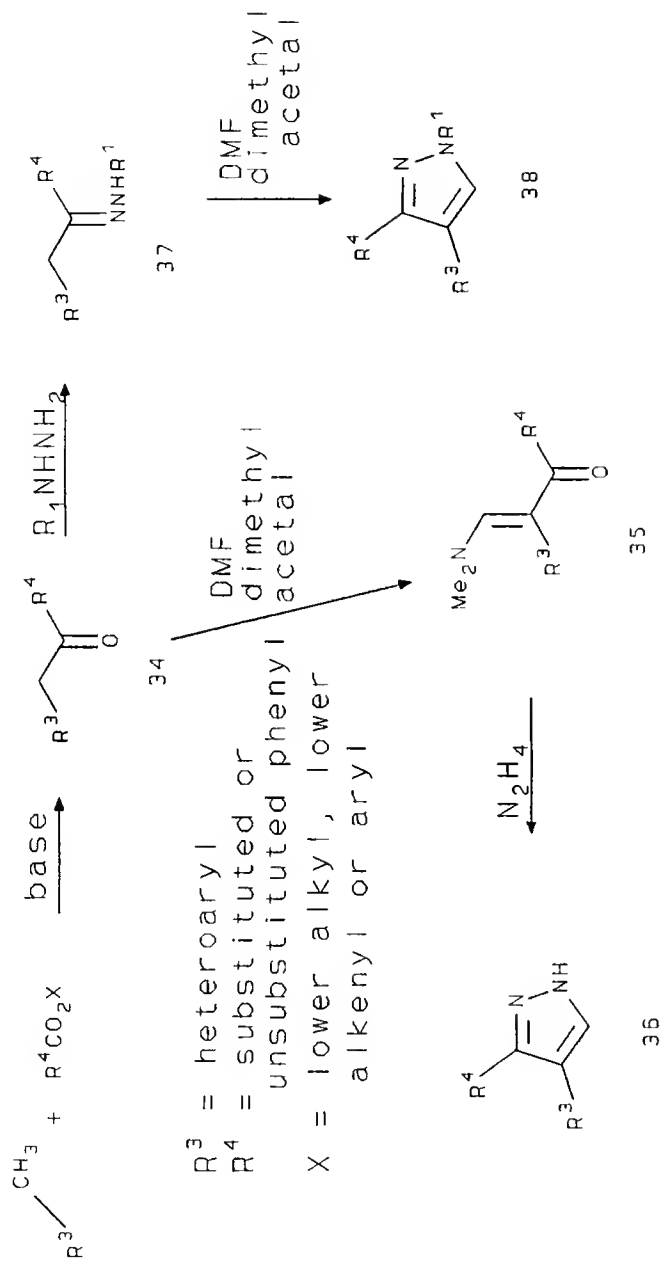
X = halyl, alkyl

R<sup>1</sup> = Me, CH<sub>2</sub>CH<sub>2</sub>OH

R<sup>4</sup> = cyclopropyl, 4-pyridyl,  
4-imidazolyl

Scheme V shows the two step synthesis of the 3-substituted 4-pyridyl-5-arylpyrazoles **33** of the present invention by cyclization of hydrazone dianions with carboxylates. In step 1, the reaction of substituted pyridylmethyl ketones **31** (prepared, for example, as later described in Scheme IX) with hydrazines in the presence of solvents such as ethanol gives ketohydrazones **32**. Examples of suitable hydrazines include, but are not limited to, phenylhydrazine and p-methoxyphenylhydrazine. In step 2, the hydrazones **32** are treated with two equivalents of a base such as sodium bis(trimethylsilyl)amide in a suitable solvent such as tetrahydrofuran to generate dianions. This reaction may be carried out at temperatures of about 0 °C or lower. In the same step, the dianions then are condensed with esters such as methyl isonicotinate, methyl cyclopropanecarboxylate, to give the desired pyrazoles

33. It may be necessary to treat the product from this step with a dehydrating agent, such as a mineral acid, to produce the target pyrazole in some instances.



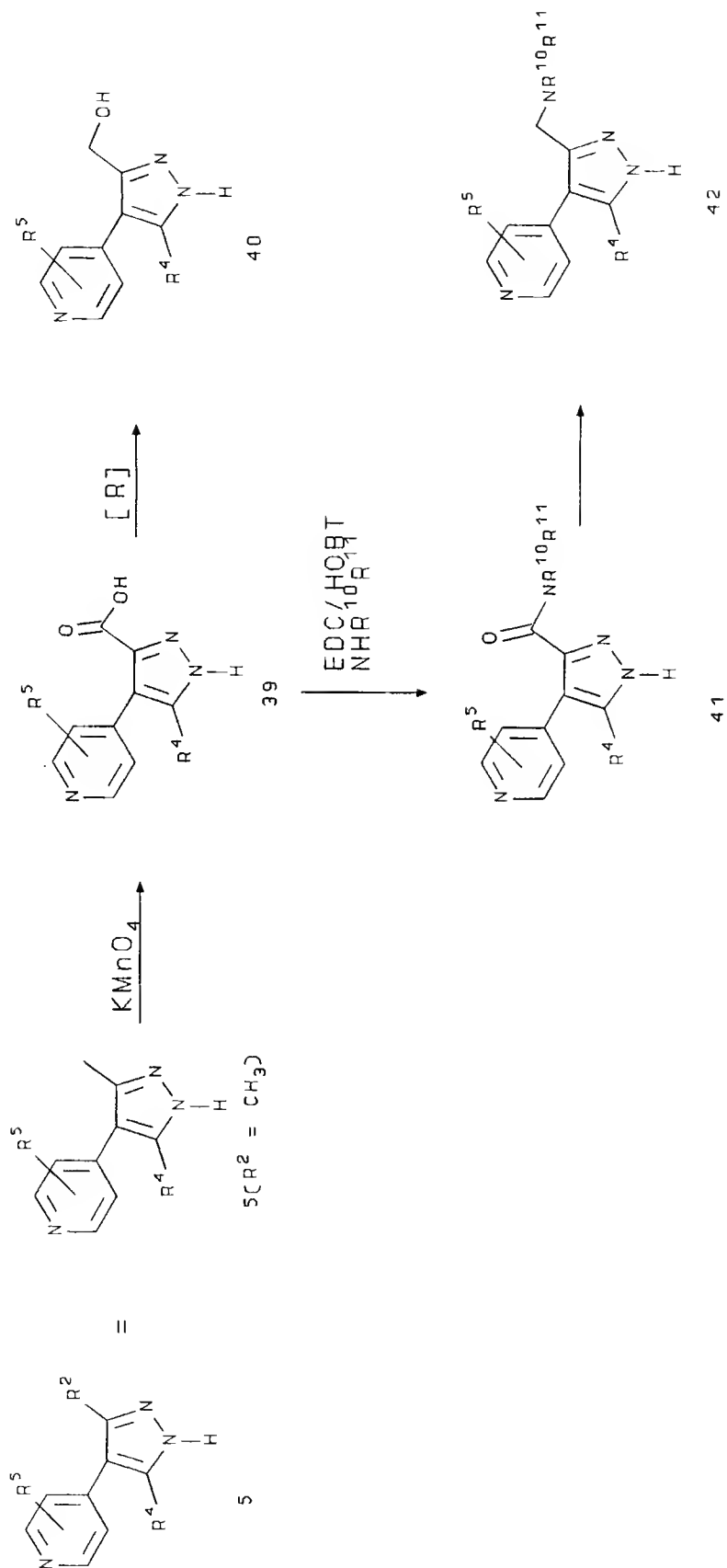
Scheme VI shows an alternative method for synthesizing pyrazoles which are unsubstituted at the 5 position of the ring. In accordance with this method, a heteroarylmethyl ketone **34** is synthesized by first treating a heteroarylmethane with a strong base such as lithium hexamethyldisilazide or lithium diisopropylamide. Examples of suitable heteroarylmethanes are 4-methylpyridine, 4-methylpyrimidine, 2,4-dimethylpyridine, 2-chloro-4-methylpyrimidine, 2-chloro-4-methylpyridine and 2-fluoro-4-methylpyridine. The resulting heteroarylmethyl lithium species is then reacted with a substituted benzoate ester to produce ketone **34**. Examples of suitable benzoate esters are methyl and ethyl p-fluorobenzoate and ethyl and methyl p-chlorobenzoate. Ketone **34** is converted to the aminomethylene derivative **35** by reaction with an aminomethylenating agent such as dimethylformamide dimethyl acetal or tert-butoxybis(dimethylamino)methane. Ketone **35** is converted to pyrazole **36** by treatment with hydrazine.

A modification of this synthetic route serves to regioselectively synthesize pyrazole **38** which contains a substituted nitrogen at position 1 of the ring. Ketone **34** is first converted to hydrazone **37** by reaction with the appropriate substituted hydrazine. Examples of suitable hydrazines are N-methylhydrazine and N-(2-hydroxyethyl)hydrazine. Reaction of hydrazone **37** with an aminomethylenating agent produces pyrazole **38**. Examples of suitable aminomethylenating agents include dimethylformamide dimethyl acetal and tert-butoxybis(dimethylamino)methane.

In cases where the R<sup>3</sup> substituent of pyrazoles **36** and **38** bears a leaving group such as a displaceable halogen, subsequent treatment with an amine produces an amino-substituted heteroaromatic derivative. Examples of such amines include benzylamine, cyclopropylamine and ammonia.

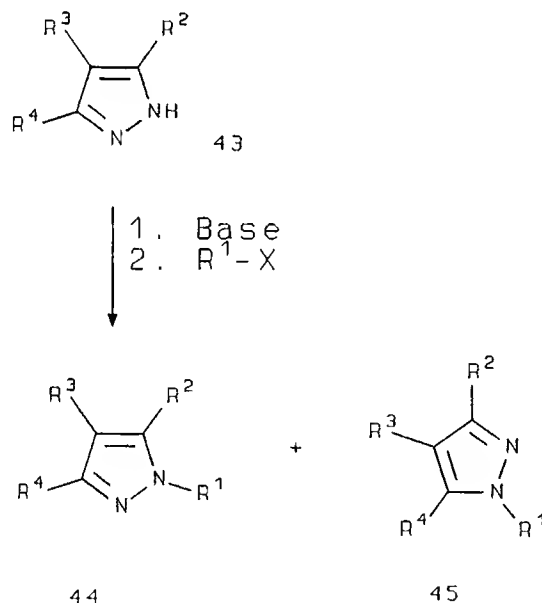
The leaving group may also be replaced with other nucleophiles such as mercaptides and alkoxides. Examples of substitutable R<sup>3</sup> groups include, but are not limited to, 2-chloropyridinyl and 2-bromopyridinyl groups.

**SCHEME VII**



Scheme VII describes the preparation of derivatives from pyrazole 5 (prepared in accordance with Scheme I) when  $R^2 = CH_3$ . Oxidation of pyrazole 5 gives carboxylic acid 39, which is then reduced to hydroxymethyl compound 40, or coupled with amine  $NR^{10}R^{11}$  (wherein  $R^{10}$  and  $R^{11}$  are independently selected, for example, from hydrogen, alkyl and aryl, or together with the nitrogen atom to which they are attached form a 4-8 membered ring that may contain one or more additional heteroatoms selected from oxygen, nitrogen or sulfur) to form amide 41 followed by reduction to generate amine derivative 42.

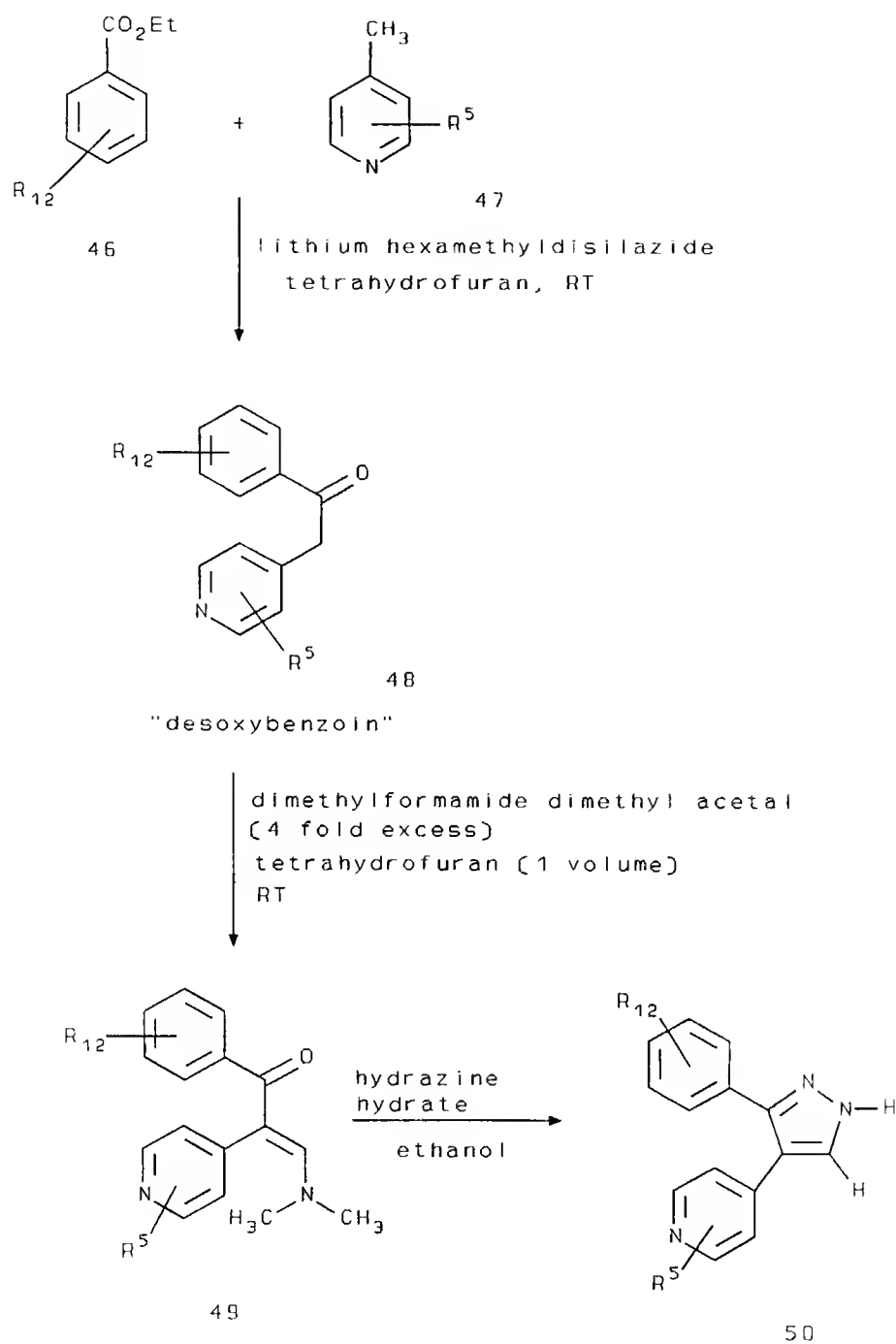
#### SCHEME VIII



Scheme VIII illustrates the synthesis of pyrazoles 44 and 45 from pyrazole 43. The alkylation of the ring nitrogen atoms of pyrazole 43 can be accomplished using conventional techniques. Treatment of pyrazole 43 with an appropriate base (for example, sodium hydride) followed by treatment with an alkyl halide (for example,  $CH_3I$ ) yields a mixture of isomers 44 and 45.

#### SCHEME IX

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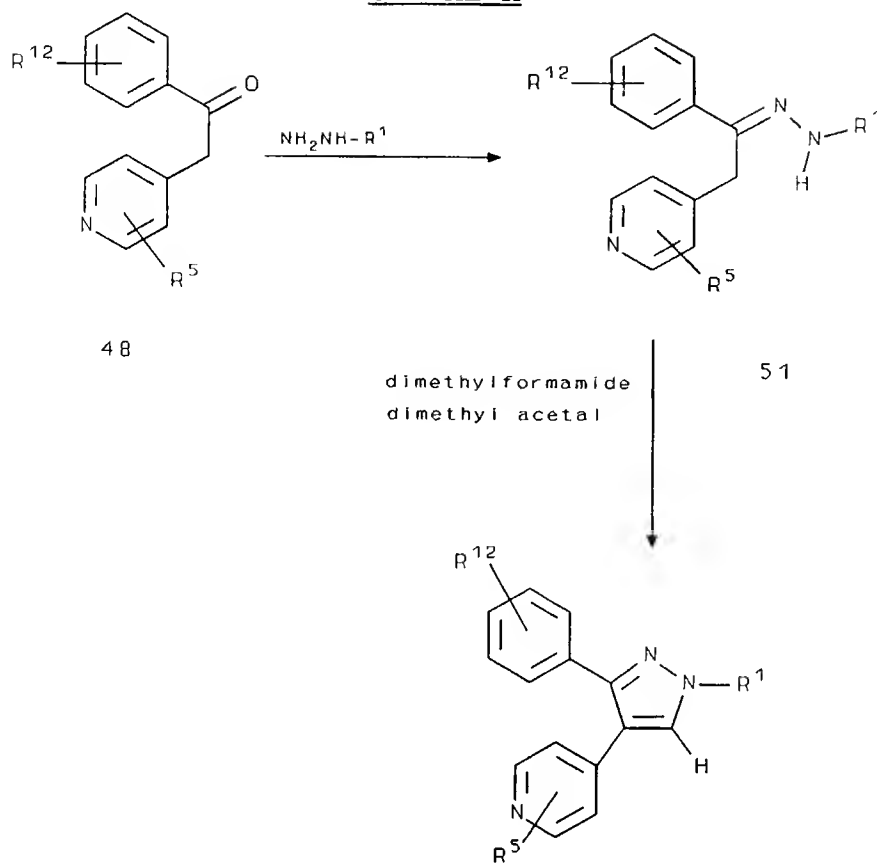




Scheme IX illustrates the synthesis of 3-aryl-4-pyridyl-pyrazoles of the present invention. Benzoate **46** is reacted with pyridine **47** in the presence of a strong base, such as an alkali metal hexamethyldisilazide (preferably sodium hexamethyldisilazide or lithium hexamethyldisilazide), in a suitable solvent, such as tetrahydrofuran, to give desoxybenzoin **48**. Desoxybenzoin **48** is then converted to ketone **49** by treatment with an excess of dimethylformamide dimethyl acetal. Ketone **49** is then reacted with hydrazine hydrate in a suitable solvent such as ethanol to yield pyrazole **50**. In Scheme IX,  $R^{12}$  represents one or more radicals independently selected from the optional substituents previously defined for  $R^4$ . Preferably,  $R^{12}$  is hydrogen, alkyl, halo, trifluoromethyl, methoxy or cyano, or represents methylenedioxy.

The 3-aryl-4-pyrimidinyl-pyrazoles of the present invention can be synthesized in the manner of Scheme IX by replacing pyridine **47** with the corresponding pyrimidine. In a similar manner, Schemes X through XVII can be employed to synthesize 3-aryl-4-pyrimidinyl-pyrimidines corresponding to the 3-aryl-4-pyrimidinyl-pyrazoles shown in those schemes.

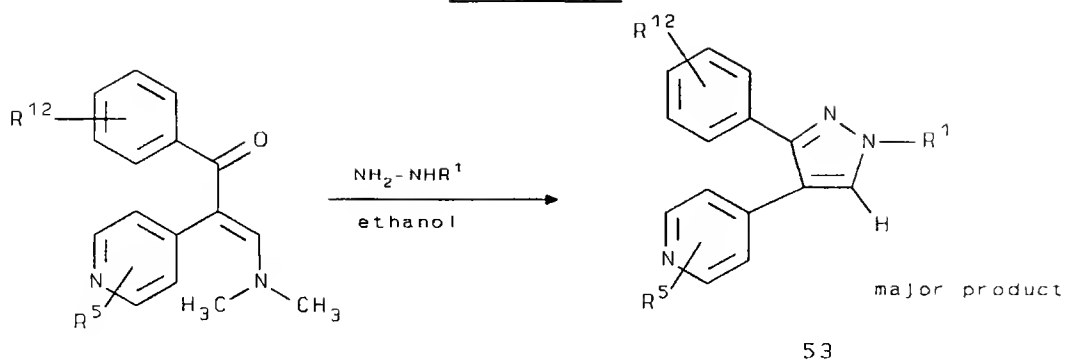
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SCHEME X

Scheme X illustrates one variation of Scheme IX that can be used to synthesize 3-aryl-4-pyridyl-pyrazoles that are further substituted on the nitrogen atom at position 1 of the pyrazole ring. If desoxybenzoin **48** (prepared in accordance with Scheme IX) instead is first converted to hydrazone **51** by treatment with hydrazine and hydrazone **51** is then treated with dimethylformamide dimethyl acetal, then the resulting product is pyrazole **52**.

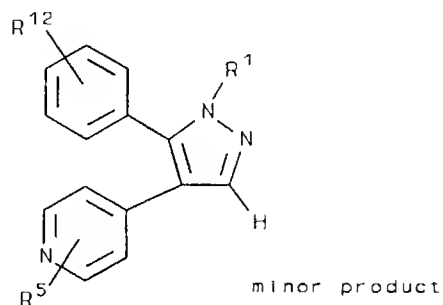
Schemes XI through XVIII illustrate further modifications that can be made to Scheme IX to synthesize other 3-aryl-4-pyridyl-pyrazoles having alternative substituents.

188

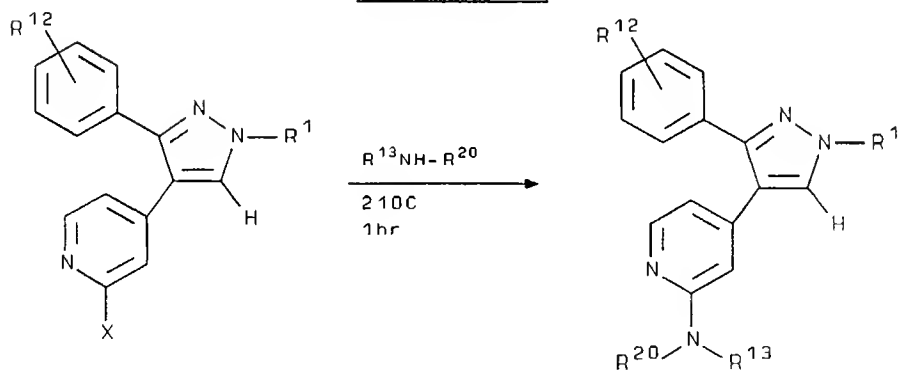
SCHEME XI

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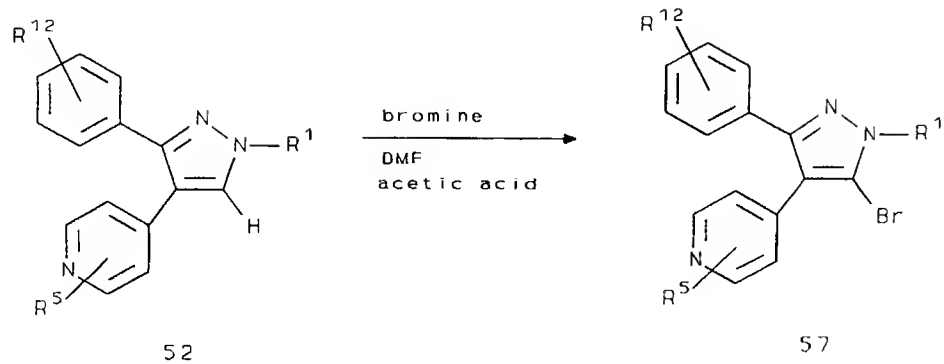
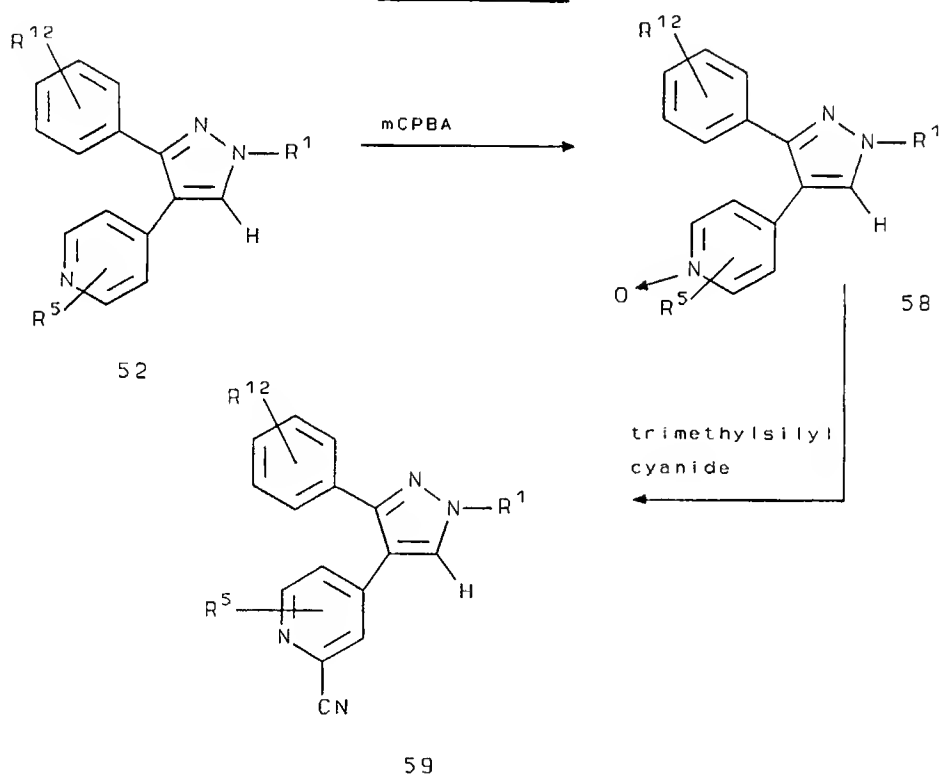
SCHEME XII

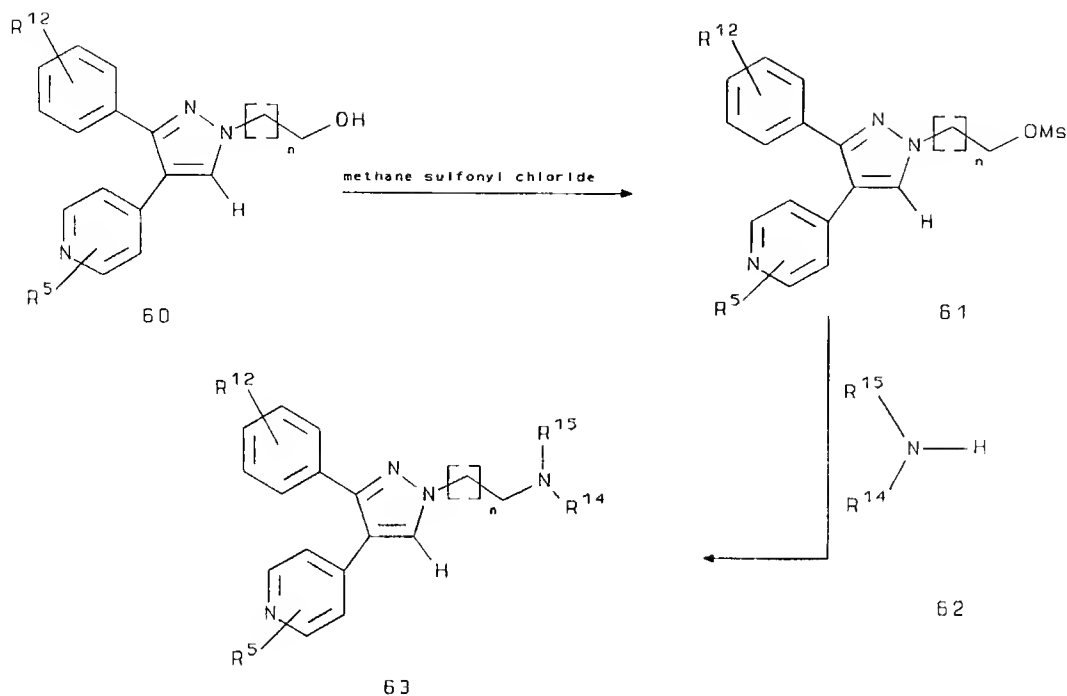
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In Scheme XII, X is chloro, fluoro or bromo;  $\text{R}^{13}$  is, for example, hydrogen, alkyl, phenyl, aralkyl, heteroarylalkyl, amino or alkylamino; and  $\text{R}^{20}$  is, for example, hydrogen or alkyl.

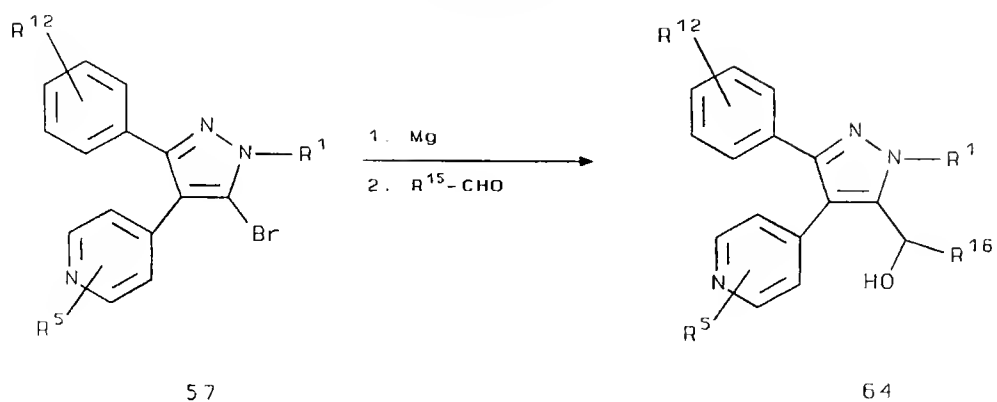
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SCHEME XIIISCHEME XIV

SCHEME XV

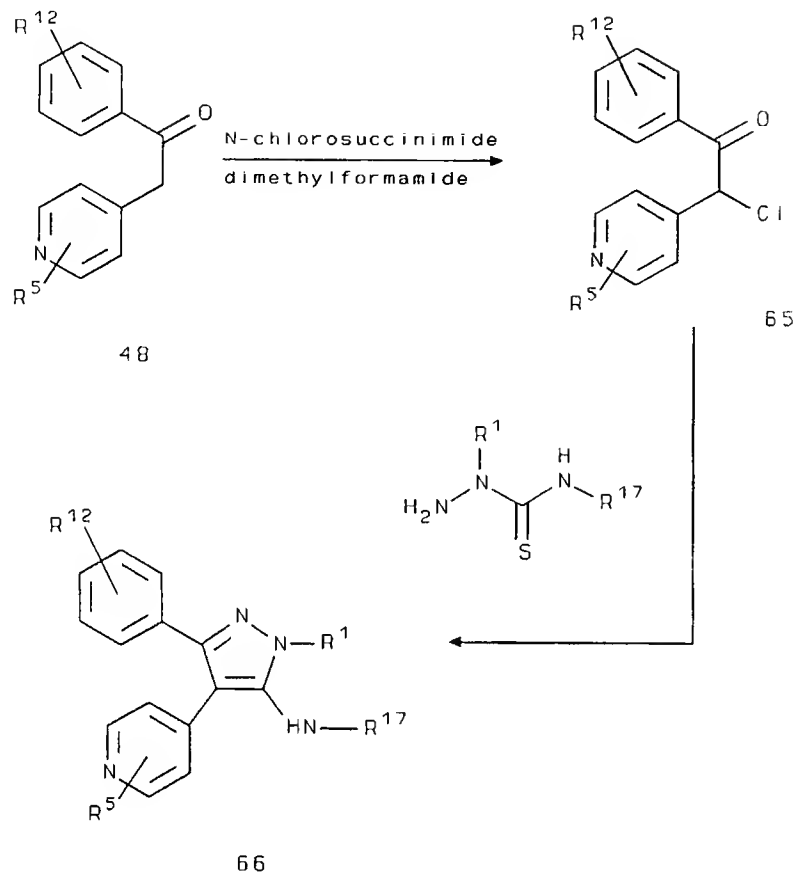
In Scheme XV,  $n$  is 1, 2, 3, 4 or 5; and  $R^{14}$  and  $R^{15}$  are independently selected from, for example, hydrogen, alkyl or aryl, or together with the nitrogen atom to which they are attached form a 4-7 membered ring that may contain one or more additional heteroatoms selected from oxygen, nitrogen or sulfur.

191

SCHEME XVI

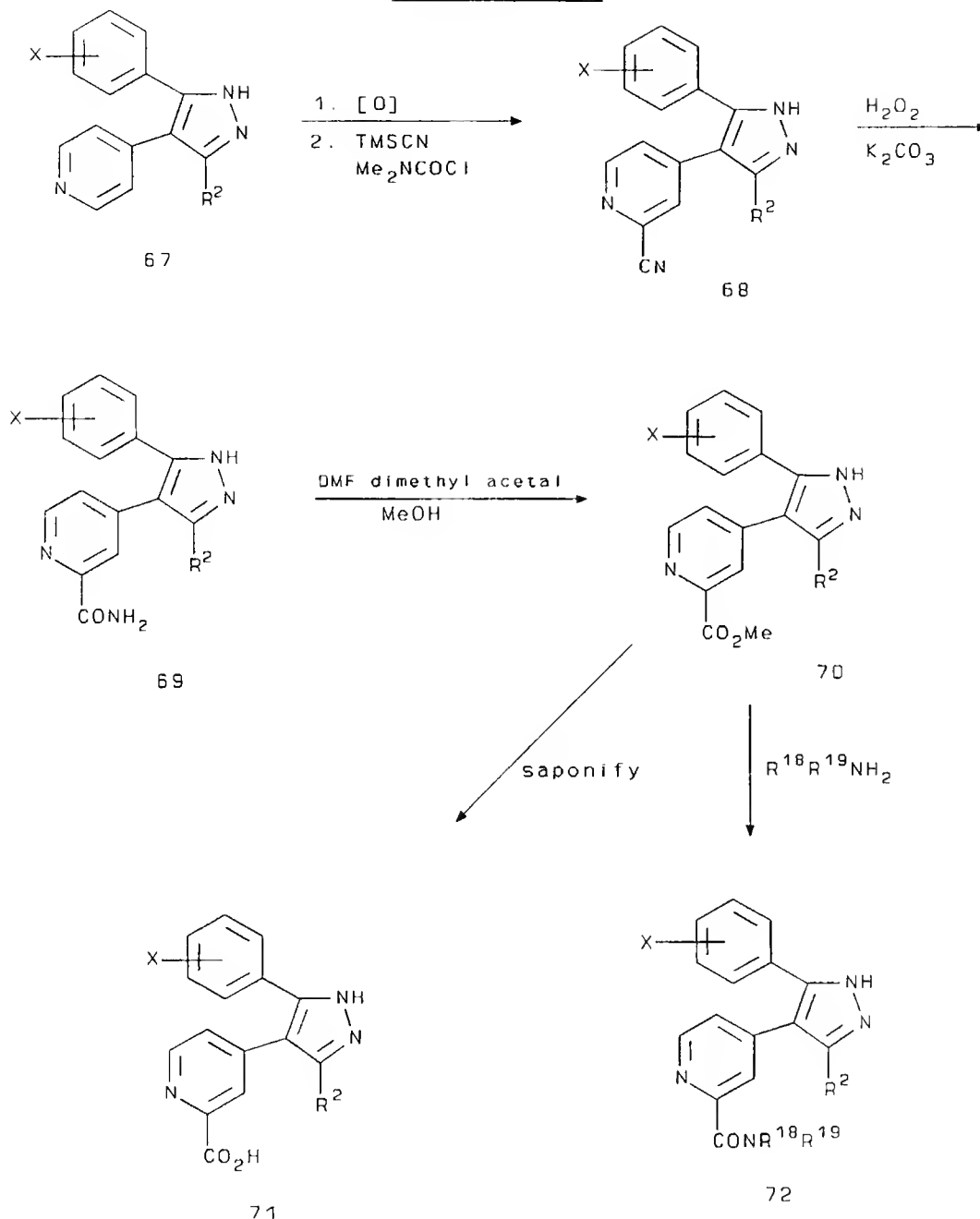
In Scheme XVI, R<sup>16</sup> is selected, for example, from hydrogen, alkyl and phenyl.

192

SCHEME XVII

In Scheme XVII,  $R^{17}$  is selected, for example, from alkyl, phenylalkyl and heterocyclalkyl.

193

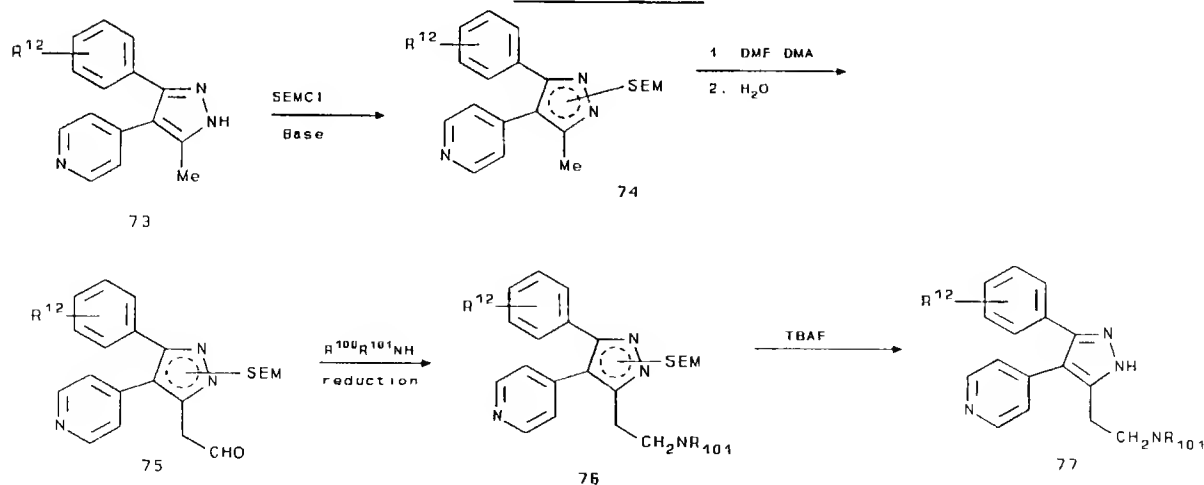
SCHEME XVIII

Compounds wherein the 2-position of the pyridine ring is substituted by a carboxyl group or a carboxyl derivative may be synthesized according to the procedures outline in Scheme XVIII. The starting pyridyl pyrazole **67** is converted to the 2-cyano derivative **68** by first conversion to its pyridine N-oxide by reaction with an oxidizing agent such as m-chloroperoxybenzoic acid.



Treatment of the pyridine N-oxide with trimethylsilyl cyanide followed by dimethylcarbamoyl chloride produces the 2-cyano compound **68**. Compound **68** is converted to its carboxamide **69** by reaction with hydrogen peroxide in the presence of a suitable base. Examples of suitable bases include potassium carbonate and potassium bicarbonate. Carboxamide **69** is converted to its methyl ester **70** by reaction with dimethylformamide dimethyl acetal in methanol. The ester **70** is converted to its carboxylic acid **71** by saponification. Typical saponification conditions include reaction with a base such as sodium hydroxide or potassium hydroxide in a suitable solvent such as ethanol or ethanol and water or methanol and water or the like. Ester **70** is also convertible to substituted amide **72** by treatment with a desired amine, such as methylamine at a suitable temperature. Temperatures may range from room temperature to 180°C. In Scheme XVIII, R<sup>18</sup> and R<sup>19</sup> are independently selected, for example, from hydrogen, alkyl and aryl, or together with the nitrogen atom to which they are attached form a 4-8 membered ring that may contain one or more additional heteroatoms selected from oxygen, nitrogen or sulfur.

# **SCHEME XIX**



The synthesis of compound **77**, wherein the amino group is extended two methylene units from the pyrazole

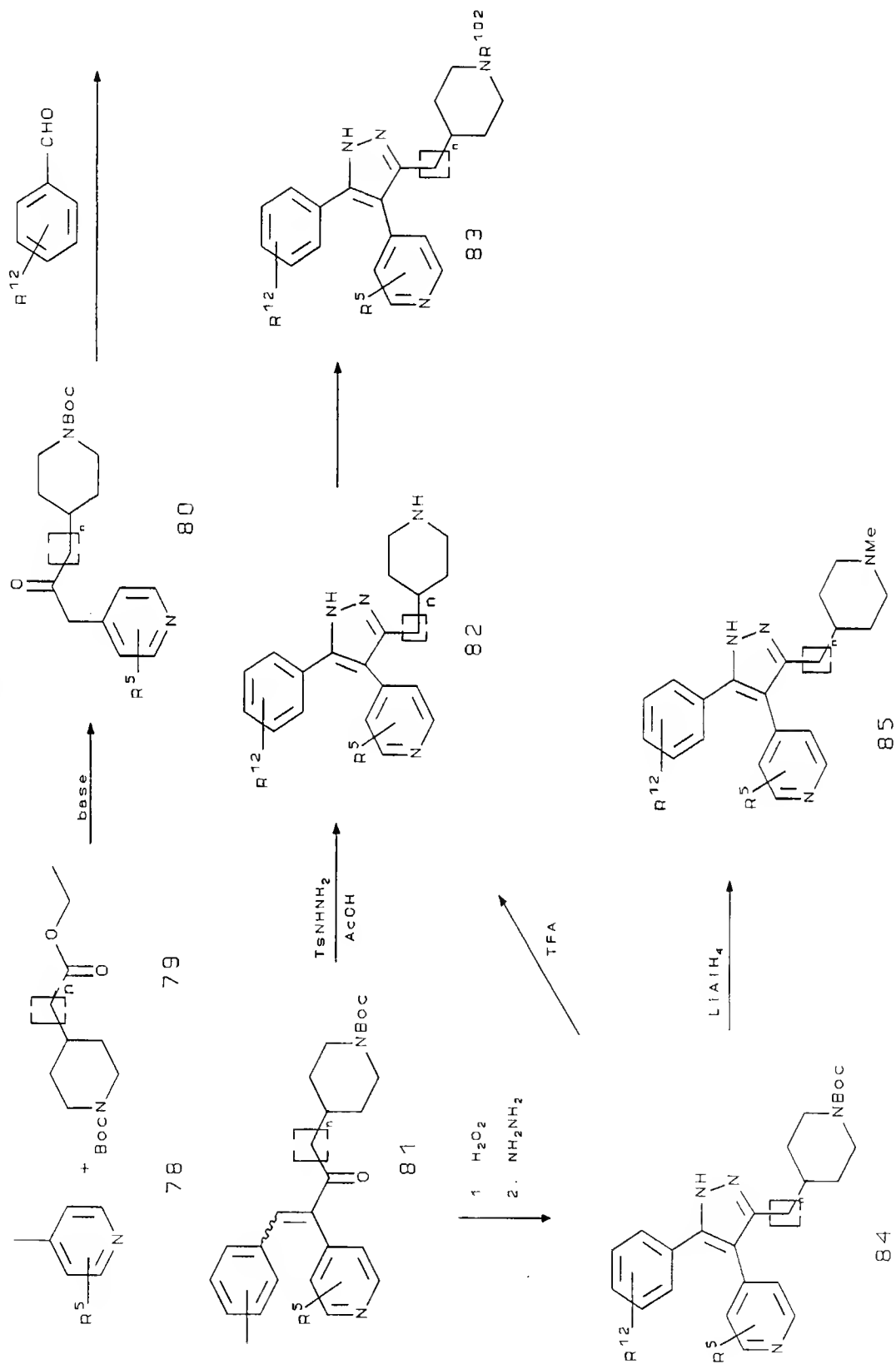
ring is illustrated in Scheme XIX above. Reaction of pyrazole 73 with a protecting reagent such as 2-(trimethylsilyl)ethoxymethyl chloride (SEM-Cl) in the presence of a base such as sodium hydride yields protected pyrazole 74. This reaction results in a mixture of regioisomers wherein the 2-(trimethylsilyl)-ethoxymethyl (SEM) group may be attached to either of the nitrogen atoms of the pyrazole ring. Alternatively, protecting reagents such as 2-methoxyethoxymethyl chloride (MEMCl) also may be used.

Reaction of compound 74 with a suitable derivative of dimethyl formamide, followed by exposure to water, leads to aldehyde 75. Examples of suitable derivatives of dimethylformamide include tert.-butoxybis(dimethylamino)methane and dimethylformamide dimethyl acetal. One skilled in the art will understand that this leads to the formation of a reactive vinyl amine as an intermediate. The reaction may be carried out in the reagent itself or in the presence of dimethylformamide as solvent. Suitable reaction temperatures range from about 50 °C to about 153 °C. The contacting of the intermediate vinyl amine with water may be carried out in solution in a suitable solvent such as methanol, ethanol, acetone, or dioxane. Alternatively, a solution of the vinyl amine in a suitable solvent may be contacted with hydrated silica gel.

Aldehyde 75 may be reductively aminated to amine 76 by reaction with the desired amine in the presence of a reducing agent. Typical reducing agents include sodium cyanoborohydride, sodium borohydride or hydrogen in the presence of a catalyst, such as a palladium/carbon catalyst or a Raney nickel catalyst, either at atmospheric pressure or in a pressurized system. An acid catalyst such as acetic acid or dilute hydrochloric acid may also be employed. The reaction may be run at ambient temperature or may be heated.

Pyrazole **77** is obtained by removal of the pyrazole nitrogen protecting group. The deprotection reaction employed will depend upon the specific protecting group removed. A 2-(trimethylsilyl)ethoxymethyl group can be removed, for example, by reaction of amine **76** with tetrabutylammonium fluoride while a 2-methoxyethoxymethyl group can be removed, for example, by acid hydrolysis.

## SCHEME XX



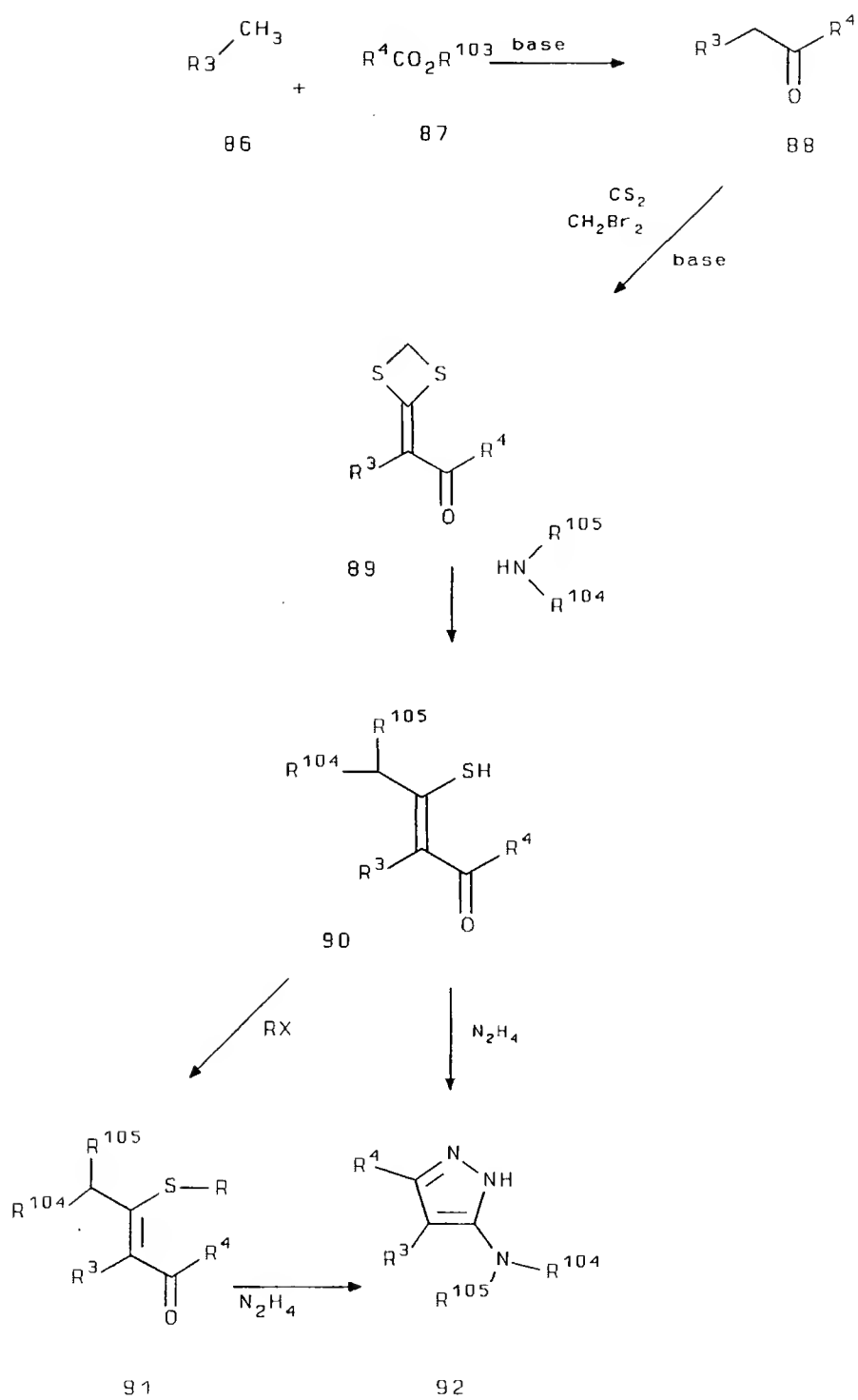
Scheme XX shows the syntheses of pyrazole **82** and its derivatives **83** and **85**. A substituted 4-picoline **78** is condensed with ethyl ester derivative **79** in the presence of a base such as lithium diisopropylamide to give ketone derivative **80**. An example of a suitable picoline is 4-picoline. Suitable ethyl ester derivatives include ethyl 4-piperidinylacetate (Compound **79**,  $n = 1$ ). Ester **79** may be synthesized, for example, by hydrogenation of ethyl 4-pyridylacetate and protection of the resulting piperidine nitrogen as the tert.-butoxycarbonyl (Boc) derivative by reaction with tert.-butoxycarbonyl chloride. The hydrogenation may be carried out, for example, at pressures from atmospheric to 100 psi. Suitable catalysts include 5% platinum on carbon. The presence of an acid such as hydrochloric acid may also improve reaction performance.

Treatment of **80** with a substituted benzaldehyde provides unsaturated ketone **81**. Pyrazole **82** may be synthesized by treatment of **81** with *p*-toluenesulfonylhydrazide in the presence of acetic acid. During this reaction, the protecting tert.-butoxycarbonyl group is removed. Derivatization of pyrazole **82** by appropriate methods as described in Scheme II for analogous piperazine derivatives gives various pyrazole derivatives **83**.

Alternatively, unsaturated ketone **81** can be converted to pyrazole **84** by first reaction with hydrogen peroxide in the presence of sodium or potassium hydroxide, followed by reaction with hydrazine. Using trifluoroacetic acid, the tert.-butoxycarbonyl group may be removed from pyrazole **84** to give pyrazole **82**.

Alternatively, the tert.-butoxycarbonyl group of **84** may be reduced with a reagent such as lithium aluminum hydride to provide the methyl derivative **85**.

199

**SCHEME XXI**

Scheme XXI shows the synthesis of pyrazoles **92**. Treatment of compound **86** with ester **87** in the presence of a base, such as sodium bis(trimethylsilyl)amide, in a suitable solvent such as tetrahydrofuran, gives ketone **88**. Substituent  $R^3$  is typically heteroaryl, preferably pyridinyl or pyrimidinyl, and more preferably 4-pyridinyl. Substituent  $R^4$  is typically aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkyl or aralkyl, and is preferably a substituted phenyl.  $R^{103}$  can be, for example, lower alkyl.

Treatment of ketone **88** with carbon disulfide, dibromomethane, and a base such as potassium carbonate in a suitable solvent such as acetone gives dithietane **89**. Other suitable bases include, but are not limited to, carbonates such as sodium carbonate, tertiary amines such as triethylamine or diazabicycloundecane (DBU), and alkoxides such as potassium tert-butoxide. Other suitable solvents include, but are not limited to, low molecular weight ketones, methyl ethyl ketone, tetrahydrofuran, glyme, acetonitrile, dimethylformamide, dimethylsulfoxide, dichloromethane, benzene, substituted benzenes and toluene.

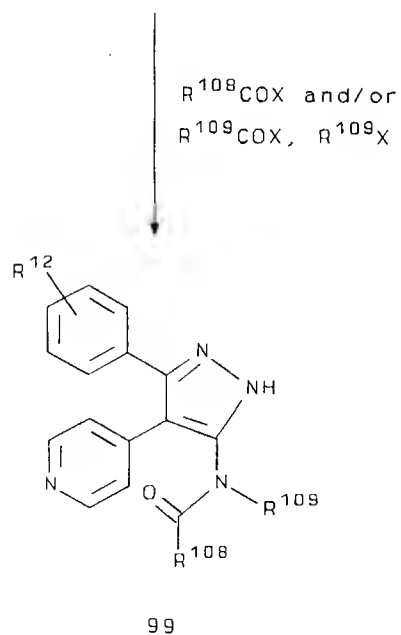
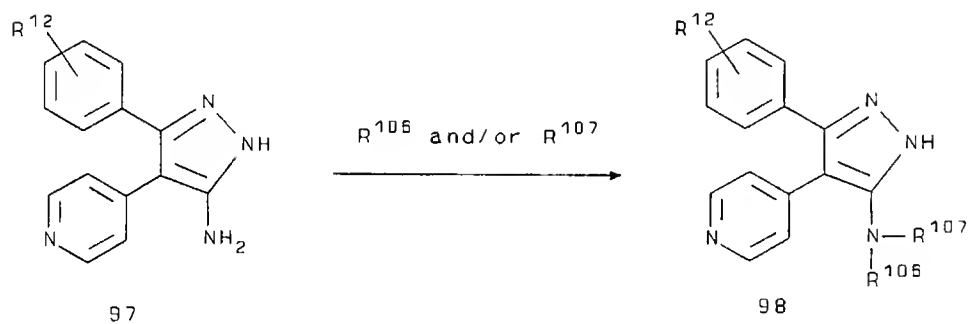
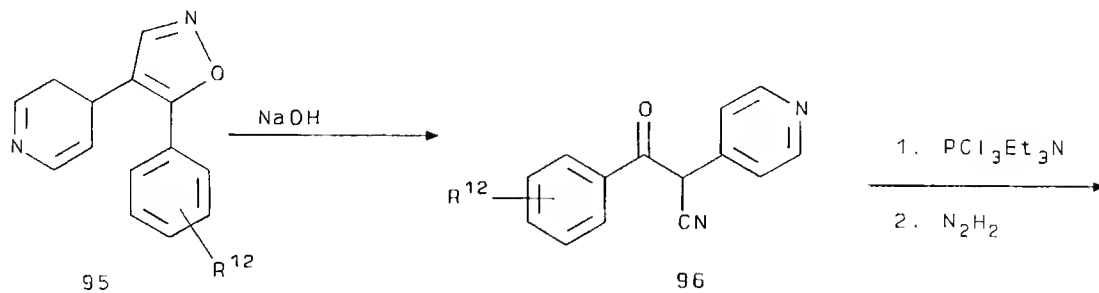
Dithietane **89** may be reacted with an appropriate amine, with or without heating, in an acceptable solvent such as toluene or acetonitrile to make thioamide **90**. Thioamide **90** is treated with hydrazine or a substituted hydrazine in an appropriate solvent such as tetrahydrofuran or an alcohol, with or without heating, to produce pyrazole **92** and/or its tautomer.

Alternatively, thioamide **90** can be reacted with an alkyl halide or a sulphonic acid ester to yield substituted thioamide **91**. Substituted thioamide **91** is treated with hydrazine or a substituted hydrazine in an appropriate solvent such as tetrahydrofuran or an alcohol, with or without heating, to produce pyrazole **92** or its tautomer.

201

$R^{104}$  and  $R^{105}$  can be independent radicals or can form a heterocyclyl ring that is optionally substituted and/or contains an additional heteroatom.



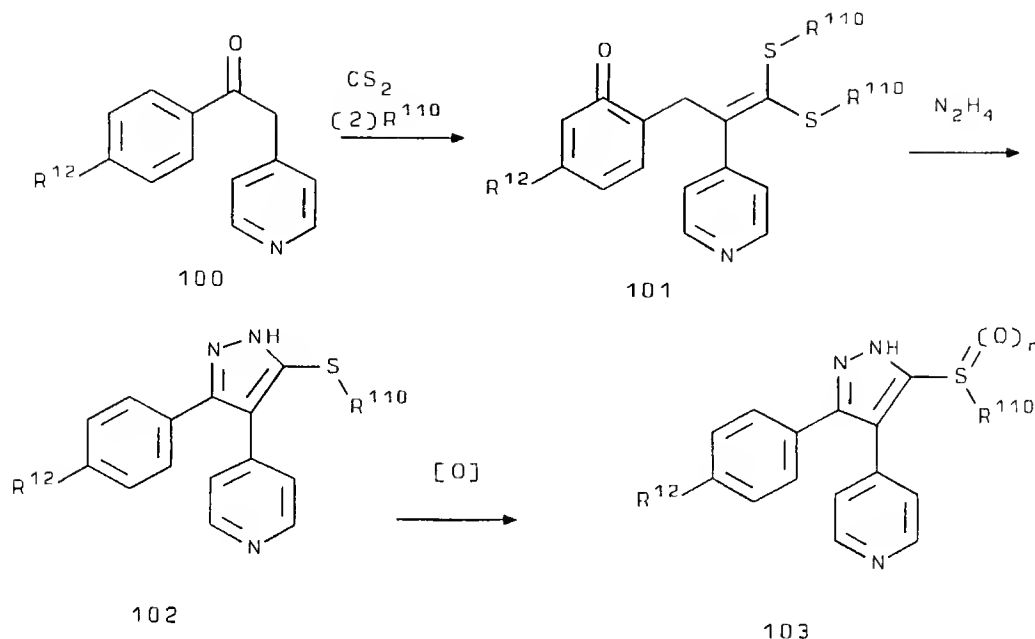


Scheme XXII shows the synthesis of substituted 5-

amino pyrazoles 98 and 99. Desoxybenzoin 93 (prepared, for example, as illustrated in Scheme IX, *supra*, or Example C-1, *infra*) is reacted with an aminomethylenating agent, such as N,N-dimethylformamide dimethyl acetal, to form aminomethylene ketone 94. Aminomethylene ketone 94 is converted to isoxazole 95 by treatment with a hydroxylamine in a suitable solvent such as ethanol. Isoxazole 95 is treated with a base, such as dilute aqueous sodium hydroxide, to form cyanoketone 96. Cyanoketone 96 is then reacted with a chlorinating agent, such as phosphorous trichloride, to form a vinyl chloride which is then treated with hydrazine hydrate (or a substituted hydrazine hydrate) to form amino pyrazole 97. Amino pyrazole 97 can be reacted further with a variety of alkyl halides, such as methyl bromoacetate, bromoacetonitrile, and chloroethylamine, to form the appropriate mono- or disubstituted, cyclic or acyclic amino pyrazole 98. Typical R<sup>106</sup> and R<sup>107</sup> substituents include, for example, hydrogen and alkyl. In addition, amino pyrazole 97 can be reacted further with a variety of acylating agents, such as benzyliminodiacetic acid and N,N-dimethylglycine, to give the corresponding mono- or disubstituted, cyclic or acyclic amide or imide 99. Typical R<sup>108</sup> and R<sup>109</sup> substituents include, for example, hydrogen, alkyl and acyl.

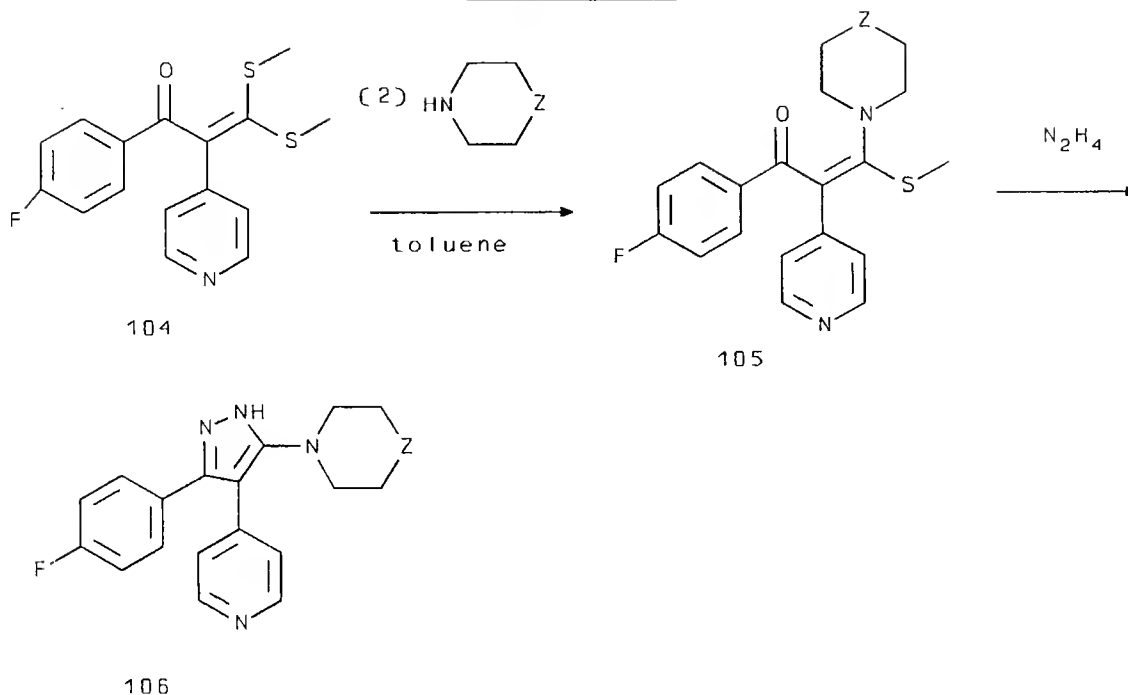
204

## SCHEME XXIII



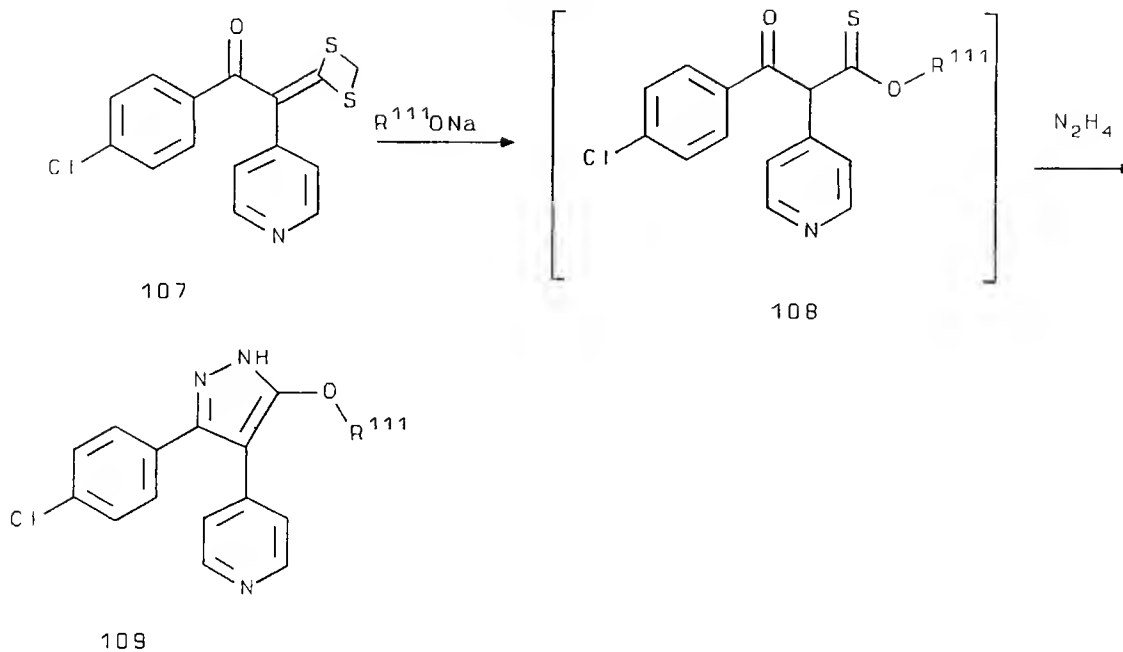
Scheme XXIII shows the synthesis of sulfoxide/sulfone 103. Ketone 100, wherein X is preferably halo such as fluoro or chloro, in a solvent, such as tetrahydrofuran, is treated with a suitable base, such as sodium hydride or potassium t-butoxide, to yield an enolate intermediate. The enolate intermediate is reacted with carbon disulfide and then alkylated with an appropriate alkylating agent, such as methyl iodide, benzyl bromide, or trimethylsilylchloride, to form dithioketene acetal 101. Dithioketene acetal 101 can be cyclized to pyrazole 102 using hydrazine, or its hydrate (or a substituted hydrazine or its hydrate), in a suitable solvent, such as tetrahydrofuran or ethanol. Pyrazole 102 is then treated with an oxidizing agent, such as potassium peroxymonosulfate, ammonium persulfate, or 3-chloroperoxybenzoic acid, to generate sulfoxide 103 (n=1) and/or sulfone 103 (n=2).

205

SCHEME XXIV

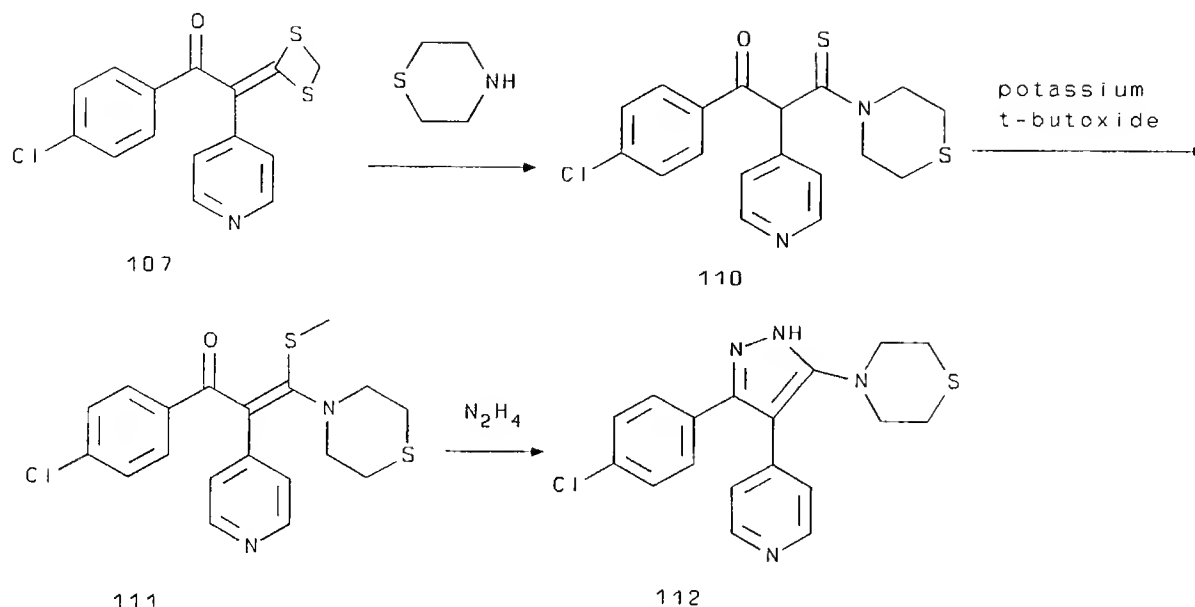
Scheme XXIV shows the synthesis of pyrazole 106. Dithioketene acetal 104 in a suitable solvent, such as toluene, is combined with a secondary amine, wherein Z is preferably S or  $-NCH_3$ , and heated to about 80-110 °C. After the solution has been heated for several hours, any insoluble bis substituted material may be removed by filtration. Mono substituted product 105 is then reacted with hydrazine, or its hydrate (or a substituted hydrazine or its hydrate), in a solvent, such as tetrahydrofuran or ethanol, at ambient up to reflux temperatures, to form pyrazole 106.

206

SCHEME XXV

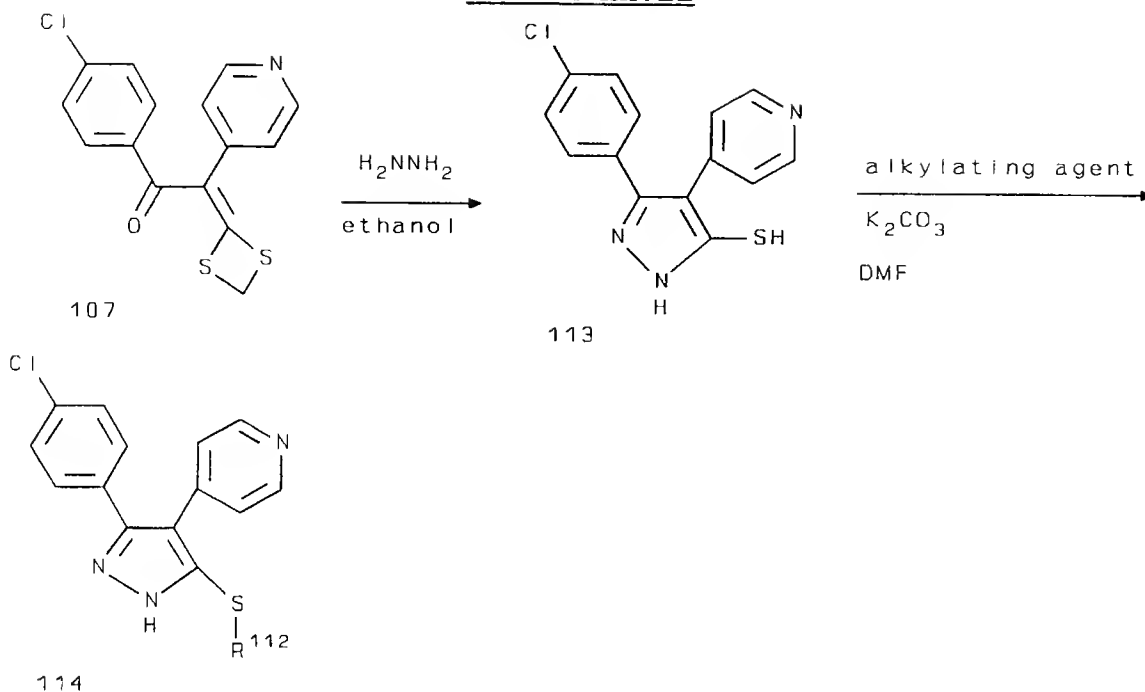
Scheme XXV shows the synthesis of pyrazole **109**. Dithietane **107** is added to a solution of a sodium or potassium alkoxide in tetrahydrofuran. The alkoxide may be generated by treating an alcohol, in tetrahydrofuran, with a suitable base, such as sodium hydride, sodium hexamethyldisilazide, or potassium hexamethyldisilazide. The reaction mixture is stirred from 4 to 72 hours at room temperature. The resulting thionoester **108** is reacted with hydrazine, or its hydrate (or a substituted hydrazine or its hydrate), in ethanol, methanol, or tetrahydrofuran at room temperature for about 2-18 hours to generate pyrazole **109**.

207

SCHEME XXVI

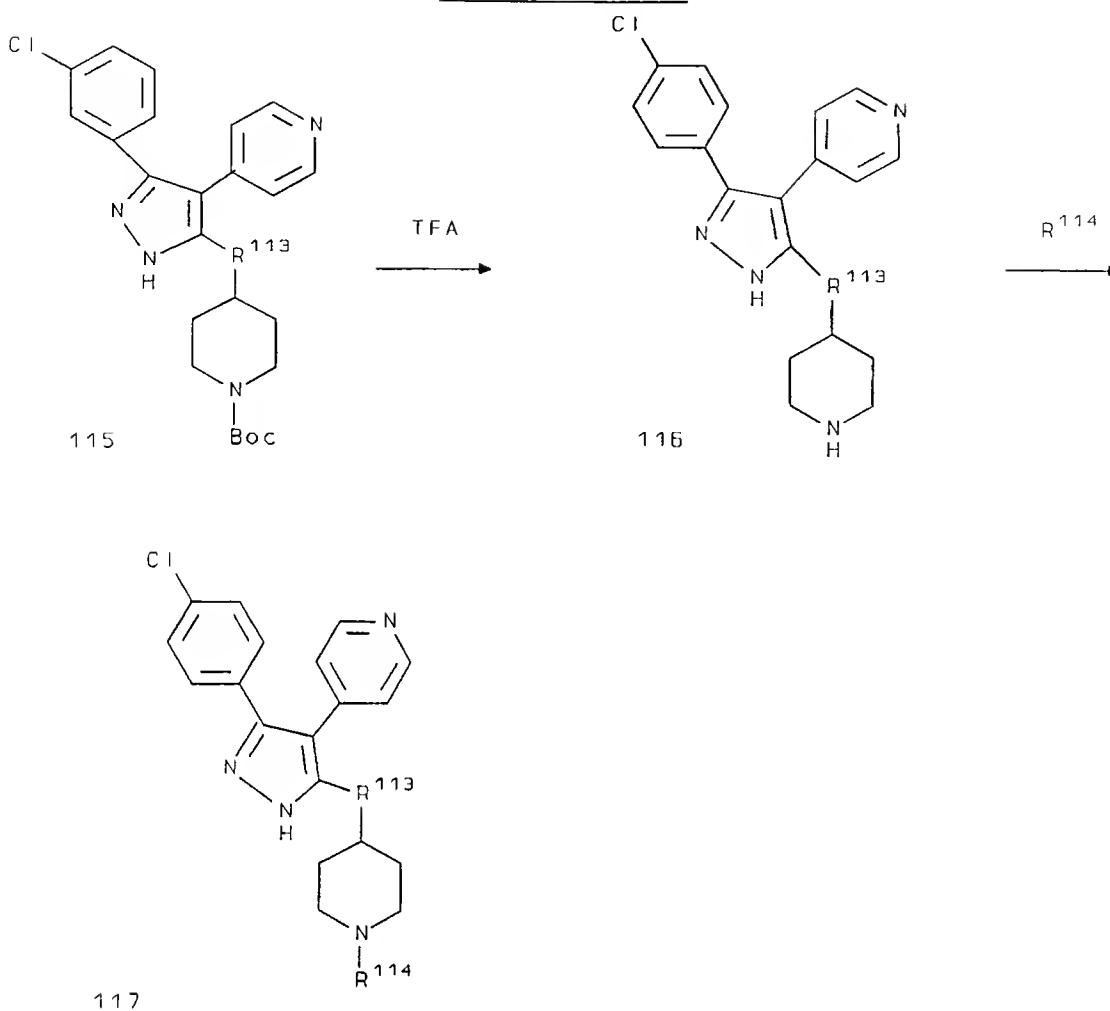
Scheme XXVI shows the synthesis of pyrazole 112. To dithietane 107 in a suitable solvent, such as toluene, is added an amine, such as thiomorpholine and heated to about 80-110 °C, to form thioamide 110. Thioamide 110 may be isolated or used directly in the next reaction step. To thioamide 110 in tetrahydrofuran is added a suitable base, such as potassium t-butoxide, and the resulting thiol anion alkylated with iodomethane to form alkylated thioamide 111. Alkylated thioamide 111 can be cyclized with hydrazine (or substituted hydrazine), in a solvent, such as tetrahydrofuran or ethanol, to generate pyrazole 112.

208

SCHEME XXVII

Scheme XXVII shows the synthesis of pyrazole 114. Dithietane 107 in a suitable solvent, such as tetrahydrofuran or ethanol, is reacted with hydrazine, or its hydrate (or a substituted hydrazine or its hydrate), at room temperature up to the reflux temperature of the solvent to generate thiopyrazole 113. The thiol group of thiopyrazole 113 may be alkylated with a variety of alkylating agents, such as alkyl halides or Michael acceptors, including, but not limited to, methyl chloroacetate, ethyl acrylate, and benzyl bromide, in the presence of a suitable base such as potassium carbonate, sodium ethoxide or triethylamine, in a solvent such as dimethylformamide or ethanol to generate pyrazole 114.

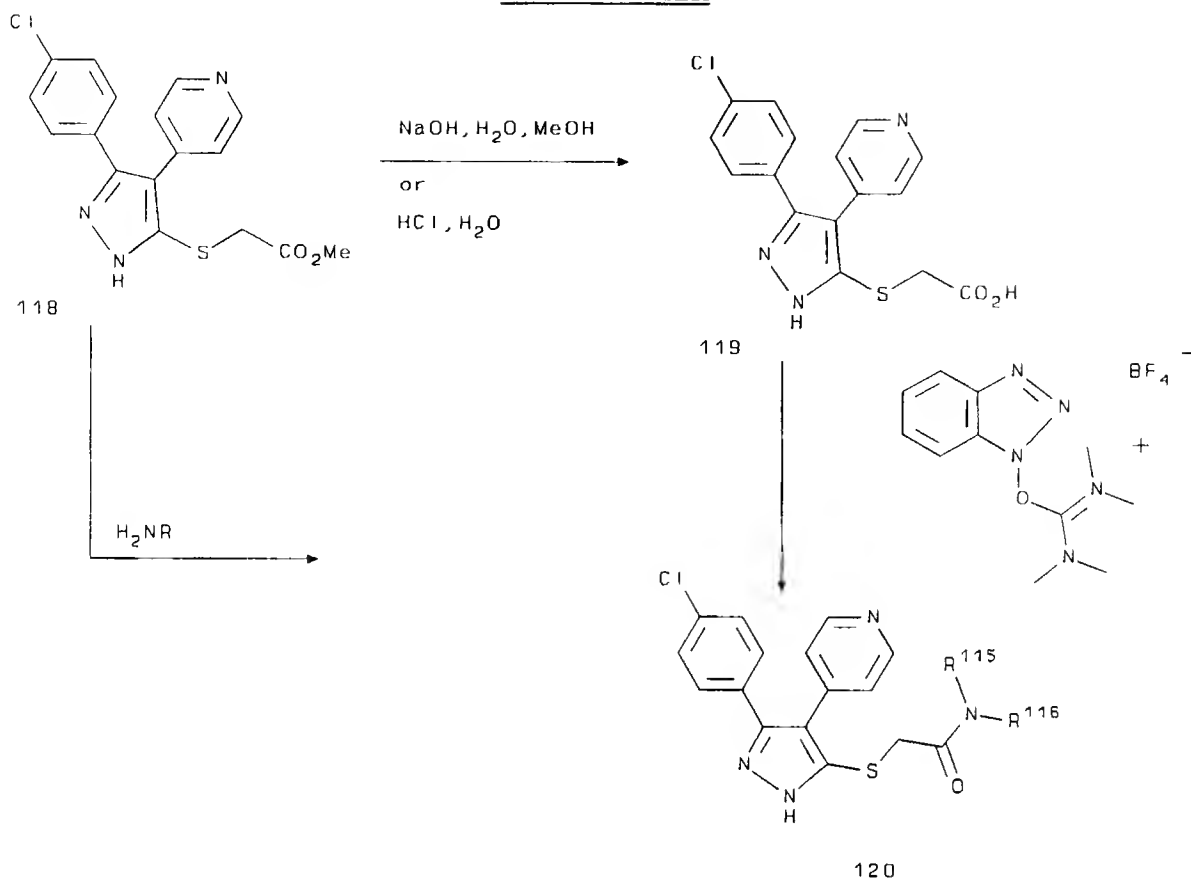
209

SCHEME XXVIII

Scheme XXVIII shows the synthesis of pyrazole 117. Pyrazoles containing acid labile amine protecting groups, such as pyrazole 115, may be treated with a suitable acid catalyst, such as trifluoroacetic acid in dichloromethane or HCl in ethanol or dioxane to yield amine 116. Amine 116 can then be acylated or alkylated by methods known to one of ordinary skill in the art, such as reacting amine 116 with a reagent such as acetyl chloride or methyl iodide in the presence of a suitable base, such as potassium carbonate or triethylamine. In addition, N-methylation can be performed directly, using formaldehyde and formic acid in ethanol/water at reflux to give pyrazole 117 wherein R<sup>114</sup> is methyl.



210

SCHEME XXIX

Scheme XXIX shows the synthesis of pyrazole 120. Pyrazoles containing base labile esters, such as pyrazole 118, may be treated with a suitable base, such as, sodium hydroxide to generate free acid 119. Acid 119 can then be aminated by methods known to one of ordinary skill in the art, such as treating acid 119 with a suitable coupling reagent, such as 1-(3-dimethylaminopropyl)3-ethylcarbodiimide hydrochloride or O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate, with or without catalysts, such as 1-hydroxybenzotriazole or N-hydroxysuccinimide, and an appropriate amine. In addition, amidation can be performed directly, by treating the methyl ester with an appropriate amine, for example N-methylpiperazine, in a suitable solvent such as dimethylformamide or methanol, at a temperature from room temperature up to reflux to generate pyrazole 120.

The following examples contain detailed descriptions of the methods of preparation of compounds of Formulas I, IA, XI, X, XI, and XX. These detailed descriptions fall within the scope, and serve to exemplify, the above described General Synthetic Procedures which form part of the invention. These detailed descriptions are presented for illustrative purposes only and are not intended as a restriction on the scope of the invention. All parts are by weight and temperatures are in Degrees centigrade unless otherwise indicated. All compounds showed NMR spectra consistent with their assigned structures. In some cases, the assigned structures were confirmed by nuclear Overhauser effect (NOE) experiments.

The following abbreviations are used:

HCl - hydrochloric acid

MgSO<sub>4</sub> - magnesium sulfate

Na<sub>2</sub>SO<sub>4</sub> - sodium sulfate

NaIO<sub>4</sub> - sodium periodate

NaHSO<sub>3</sub> - sodium bisulfite

NaOH - sodium hydroxide

KOH - potassium hydroxide

P<sub>2</sub>O<sub>5</sub> - phosphorus pentoxide

Me - methyl

Et - ethyl

MeOH - methanol

EtOH - ethanol

HOAc (or AcOH) - acetic acid

EtOAc - ethyl acetate

H<sub>2</sub>O - water

H<sub>2</sub>O<sub>2</sub> - hydrogen peroxide

CH<sub>2</sub>Cl<sub>2</sub> - methylene chloride

K<sub>2</sub>CO<sub>3</sub> - potassium carbonate

KMnO<sub>4</sub> - potassium permanganate

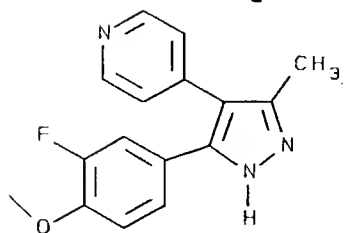
NaHMDS - sodium hexamethyldisilazide

DMF - dimethylformamide

EDC - 1-(3-dimethylaminopropyl)3-ethylcarbodiimide

hydrochloride  
HOBT - 1-hydroxybenzotriazole  
mCPBA - 3-chloroperoxybenzoic acid  
Ts - tosyl  
TMSCN - trimethylsilyl cyanide  
Me<sub>2</sub>NCOCl - N,N-dimethylcarbamoyl chloride  
SEM-Cl - 2-(trimethylsilyl)ethoxymethyl chloride  
h - hour  
hr - hour  
min - minutes  
THF - tetrahydrofuran  
TLC - thin layer chromatography  
DSC - differential scanning calorimetry  
b.p. - boiling point  
m.p. - melting point  
eq - equivalent  
RT - room temperature  
DMF DMA - dimethylformamide dimethyl acetal  
TBAF - tetrabutylammonium fluoride  
Boc - tert.-butoxycarbonyl  
DBU - diazabicycloundecane  
DMF(OMe)<sub>2</sub> - N,N-dimethylformamide dimethyl acetal  
Et<sub>3</sub>N - triethylamine  
TMSCl - trimethylsilylchloride  
TFA - trifluoroacetic acid  
TBTU - O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium  
tetrafluoroborate  
psi - pounds per square inch  
ESHRMS - electron spray high resolution mass spectroscopy

213

**Example A-1**

4-[5-(3-fluoro-4-methoxyphenyl)-3-methyl-1H-pyrazol-4-yl]pyridine

Step 1: Preparation of 4-(3-fluoro-4-methoxyphenyl)-3-pyridyl-3-butene-2-one

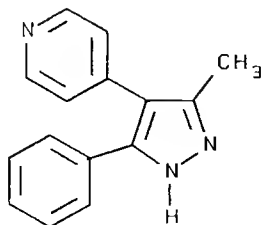
A solution of 4-pyridylacetone (1.0 g, 7.4 mmol), 3-fluoro-*p*-anisaldehyde (1.25 g, 8.1 mmol), and piperidine (0.13 g, 1.5 mmol) in toluene (50 ml) was heated to reflux. After 18 hours, the reaction was cooled to room temperature and the solvent was removed under reduced pressure. The crude product (3.0 g) was purified by column chromatography (silica gel, 65:35 ethyl acetate/hexane) to give 4-(3-fluoro-4-methoxyphenyl)-3-pyridyl-3-butene-2-one as a pale yellow solid (1.60 g, 80%).

Step 2: Preparation of 4-[5-(3-fluoro-4-methoxyphenyl)-3-methyl-1H-pyrazol-4-yl]pyridine

To a solution of 3-pyridyl-4-(3-fluoro-4-methoxyphenyl)-3-butene-2-one (step 1) (0.99 g, 3.65 mmol) in acetic acid (25 ml), *p*-toluenesulfonyl hydrazide (0.68 g, 3.65 mol) was added. The reaction solution was heated to reflux for 6 hours. Acetic acid was removed by distillation from the reaction solution. The resulting residue was diluted with CH<sub>2</sub>Cl<sub>2</sub> (150 ml), washed with H<sub>2</sub>O (2x100 ml), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The crude product (1.5 g) was purified by chromatography (silica gel, ethyl acetate) to give 4-[5-(3-fluoro-4-methoxyphenyl)-3-methyl-1H-pyrazol-4-yl]pyridine as a pale yellow solid (213 mg, 20.7%): Anal. Calc'd for C<sub>16</sub>H<sub>14</sub>N<sub>3</sub>OF.0.1 H<sub>2</sub>O: C, 67.41; H, 5.02; N, 14.74. Found:

214

C, 67.37; H, 4.88; N, 14.35.

**Example A-2**

4-(3-methyl-5-phenyl-1H-pyrazol-4-yl)  
pyridine

**Step 1: Preparation of 4-pyridylacetone**

4-Pyridylacetone was prepared according to the method of Ippolito et al, U.S. Patent 4,681,944.

**Step 2: Preparation of 4-phenyl-3-(4-pyridyl)-3-buten-2-one**

Using the procedure of Example A-1, step 1, 4-pyridylacetone (step 1) (1 g, 7.4 mmol) was condensed with benzaldehyde (790 mg, 7.4 mmol) in benzene (15 mL) containing piperidine (50 mg) at reflux. The desired 4-phenyl-3-(4-pyridyl)-3-buten-2-one (1.3 g, 78 %) was obtained as a crystalline solid: m. p. 101-103 °C. Anal. Calc'd for  $C_{15}H_{13}NO$  (223.28): C, 80.69; H, 5.87; N, 6.27. Found: C, 80.59; H, 5.79; N, 6.18.

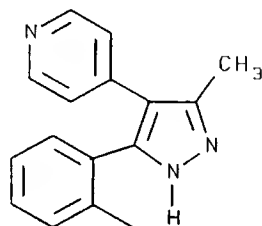
**Step 3: Preparation of 4-phenyl-3-(4-pyridyl)-3,4-epoxy-2-butanone**

Using the procedure of Example A-1, step 2, a solution of 4-phenyl-3-(4-pyridyl)-3-buten-2-one (step 2) (1.25 g, 5.6 mmol) in methanol (20 ml) was treated with 30% aqueous hydrogen peroxide (1 ml) in the presence of sodium hydroxide (230 mg, 5.7 mmol). The crude product was purified by chromatography (silica gel, 1:1 ethyl acetate/hexane) to give 4-phenyl-3-(4-pyridyl)-3,4-epoxy-2-butanone (270 mg, 20%).

Step 4: Preparation of 4-(3-methyl-5-phenyl-1H-pyrazol-4-yl)pyridine

Using the procedure of Example A-1, step 3, a solution of 4-phenyl-3-(4-pyridyl)-3,4-epoxy-2-butanone (step 3) (250 mg, 1 mmol) in ethanol (15 ml) was treated with anhydrous hydrazine (50 mg, 1.5 mmol) and heated to reflux for 4 hours. The crude product was purified by chromatography (silica gel, 1:1 acetone/hexane). The product was recrystallized from ethyl acetate and hexane to give 4-(3-methyl-5-phenyl-1H-pyrazol-4-yl)pyridine (81 mg, 35%) as a crystalline solid: m. p. 212-214 °C. Anal. Calc'd for  $C_{15}H_{13}N_3$  (235.29): C, 76.57; H, 5.57; N, 17.86. Found: C, 76.49; H, 5.42; N, 17.39.

**Example A-3**



4-[5-methyl-3-(2-methylphenyl)-1H-pyrazol-4-yl]pyridine

Step 1: Preparation of 4-(2-methylphenyl)-3-(4-pyridyl)-3-butene-2-one

A solution of 4-pyridylacetone (Example A-5, step 1) (0.75 g, 5.56 mmol), o-tolualdehyde (0.73 g, 5.56 mmol) and piperidine (100 mg) in toluene (50 ml) was heated to reflux. Water generated during the reaction was removed by a Dean-Stark trap. After heating at reflux for 5 hours, the reaction mixture was stirred at room temperature for 15 hours. The mixture was concentrated to an orange color oily residue. The crude ketone was purified by chromatography to give 4-(2-methylphenyl)-3-(4-pyridyl)-3-butene-2-one: Anal. Calc'd for  $C_{16}H_{15}NO$  (237.30): C, 80.98; H, 6.37; N, 5.90. Found: C, 80.78; H, 6.61; N, 5.85.

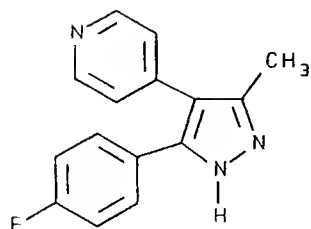
Step 2: Preparation of 4-(2-methylphenyl)-3-(4-pyridyl)-3,4-epoxy-2-butanone

To a solution of 4-(2-methylphenyl)-3-(4-pyridyl)-3-buten-2-one (step 1) (1.0g, 4.2 mmol) in methyl alcohol (18 ml), a solution of H<sub>2</sub>O<sub>2</sub> (30% by wt.) (0.95 g, 8.4 mmol) and sodium hydroxide (0.18 g 4.6 mmol) in water (4 ml) was added. The reaction was stirred at room temperature for 70 hours. After methyl alcohol was removed, water (25 ml) and ethyl acetate (100 ml) were added and the two phase mixture was stirred for 30 minutes. The layers were separated, and the aqueous layer was washed with ethyl acetate (100 ml). The combined organic layer was dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give an oil. 4-(2-Methylphenyl)-3-(4-pyridyl)-3,4-epoxy-2-butanone was isolated from the oil residue by chromatography.

Step 3: Preparation of 4-[5-methyl-3-(2-methylphenyl)1H-pyrazol-4-yl]pyridine

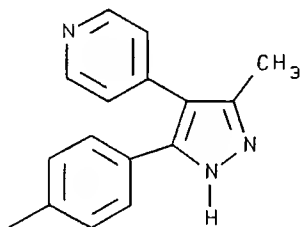
A solution of 4-(2-methylphenyl)-3-(4-pyridyl)-3,4-epoxy-2-butanone (step 2) (0.11 g, 0.434 mmol) and hydrazine hydrate (0.043 g, 0.868 mmol) in ethyl alcohol (50 ml) was heated at reflux for 20 hours. The solvent was removed and the resulting residue was purified by chromatography to give 4-[5-methyl-3-(2-methylphenyl)-1H-pyrazol-4-yl]pyridine: Anal. Calc'd for C<sub>16</sub>H<sub>15</sub>N<sub>3</sub> (249.32): C, 77.08; H, 6.06; N, 16.85. Found: C, 76.66; H, 5.91; N, 16.84.

217

**Example A-4**

4-[5-methyl-3-(4-fluorophenyl)-1H-pyrazol-4-yl]pyridine

By following the method of Example A-3 and substituting *p*-fluorobenzaldehyde for *o*-tolualdehyde, the titled compound was prepared: Anal. Calc'd for  $C_{15}H_{12}N_3F + 0.1 H_2O$ : (249.32): C, 70.63; H, 4.82; N, 16.47. Found: C, 70.63; H, 4.78; N, 16.40.

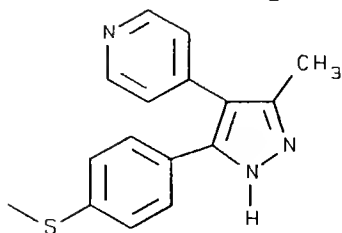
**Example A-5**

4-[5-methyl-3-(4-methylphenyl)-1H-pyrazol-4-yl]pyridine

By following the method of Example A-3 (with one minor modification: in Step 2, the preparation of the intermediate epoxide was accomplished at 0-10 °C for 1 hour, and the reaction was quenched by being partitioned between water, containing 2 eq. sodium bisulfite, and ethyl acetate) and substituting *p*-tolualdehyde for *o*-tolualdehyde, the titled product was isolated: Anal. Calc'd for  $C_{16}H_{15}N_3$  (249.32): C, 77.08; H, 6.06; N, 16.85. Found: C, 76.97; H, 6.09; N, 16.90.

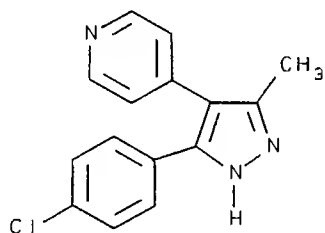


218

**Example A-6**

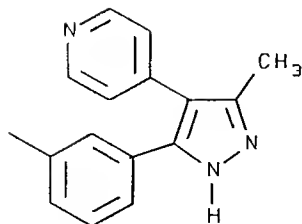
4-[5-methyl-3-[4-(methylthio)phenyl]-  
1H-pyrazol-4-yl]pyridine

By following the method of Example A-5 and substituting 4-(methylthio)benzaldehyde for *p*-tolualdehyde, the titled product was prepared: Anal. Calc'd for C<sub>16</sub>H<sub>15</sub>N<sub>3</sub>S (281.38): C, 68.30; H, 5.37; N, 14.93. Found: C, 68.34; H, 5.09; N, 14.78.

**Example A-7**

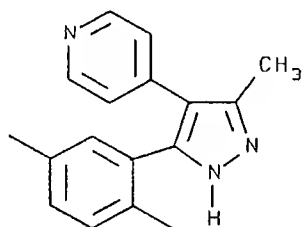
4-[3-(4-chlorophenyl)-5-methyl-1H-  
pyrazol-4-yl]pyridine

By following the method of Example A-5 and substituting *p*-chlorobenzaldehyde for *p*-tolualdehyde, the titled product was obtained. Anal. Calc'd for C<sub>15</sub>H<sub>12</sub>N<sub>3</sub>Cl (269.77): C, 66.79; H, 4.48; N, 15.58. Found: C, 66.43; H, 4.44; N, 15.78.

**Example A-8**

4-[3-methyl-5-(3-methylphenyl)-1H-pyrazol-4-yl]pyridine

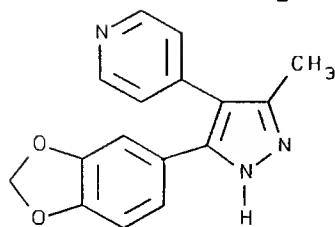
By following the method of Example A-5 and substituting *m*-tolualdehyde for *p*-tolualdehyde, the titled product was obtained: Anal. Calc'd for  $C_{16}H_{15}N_3 + 0.2H_2O$ : C, 75.98; H, 6.14; N, 16.61. Found: C, 76.06; H, 6.05; N, 16.38.

**Example A-9**

4-[5-(2,5-dimethylphenyl)-3-methyl-1H-pyrazol-4-yl]pyridine

By following the method of Example A-5 and substituting 2,5-dimethylbenzaldehyde for *p*-tolualdehyde, the titled product was obtained: Anal. Calc'd for  $C_{17}H_{17}N_3 + 0.1H_2O$ : C, 77.01; H, 6.54; N, 15.85. Found: C, 76.96; H, 6.81; N, 15.51.

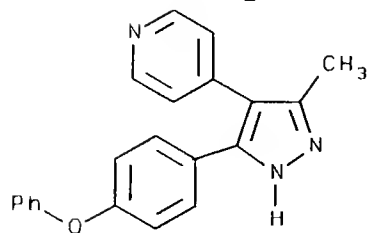
## Example A-10



4-[5-(1,3-benzodioxol-5-yl)-3-methyl-  
1H-pyrazol-4-yl]pyridine

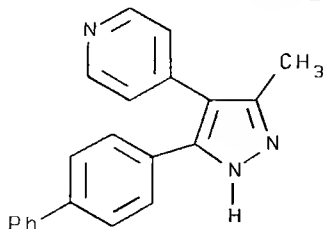
4-Pyridylacetone (1.5 g, 12 mmol), piperonal (1.6 g, 10.6 mmol), acetic acid (110 mg, 1.8 mmol), and piperidine (110 mg, 1.3 mmol) were dissolved in toluene (30 mL) and heated for 2 hours at reflux in a flask equipped with a Dean-Stark trap. The solution was cooled to room temperature, and ethyl acetate was added to precipitate a solid, which was collected on a filter plate (1.25 g). A sample (500 mg) of this solid was heated with p-toluensulfonyl hydrazide (348 mg, 1.81 mmol) in acetic acid (5 mL) at 80 °C for 1 hour. The reaction was heated to reflux for 1 hour. The reaction was cooled to room temperature and the solvent was evaporated. The residue was dissolved in ethyl acetate, washed with 5% aqueous potassium carbonate, and water. The organic layer was dried (MgSO<sub>4</sub>), filtered and evaporated to obtain a yellow solid. This solid was triturated with methylene chloride, yielding 4-[5-(1,3-benzodioxol-5-yl)-3-methyl-1H-pyrazol-4-yl]pyridine which was collected on a filter plate (220 mg, 42% yield). Anal. Calc'd for C<sub>16</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub>: C, 68.81; H, 4.69; N, 15.04. Found: C, 68.02; H, 4.54; N, 14.76. MS (M<sup>+</sup>H): 280 (base peak).

221

**Example A-11**

4-[3-methyl-5-(4-phenoxyphenyl)-  
1H-pyrazol-4-yl]pyridine

4-Pyridylacetone (1.5 g, 12 mmol), 4-phenoxybenzaldehyde 92.1 g, 10.6 mmol), acetic acid (110 mg, 1.8 mmol), and piperidine (110 mg, 1.3 mmol) were dissolved in toluene (30 mL) and heated for 2 hours at reflux in a flask equipped with a Dean-Stark trap. The solution was cooled to room temperature and ethyl acetate was added to precipitate a solid, which was collected on a filter plate. A sample (223 mg) of this solid was heated with p-toluensulfonyl hydrazide (348 mg, 1.81 mmol) in ethylene glycol with potassium hydroxide (77 mg) at 110 °C for 0.5 hour. The work up procedure was the same as that in Example A-10. 4-[3-Methyl-5-(4-phenoxyphenyl)-1H-pyrazol-4-yl]pyridine was obtained (100 mg, 66% yield): Anal. Calc'd for  $C_{21}H_{17}N_3O + 0.1 H_2O$ : C, 76.62; H, 5.27; N, 12.76. Found: C, 76.37; H, 5.19; N, 12.64. MS ( $M^+H$ ): 328 (base peak).

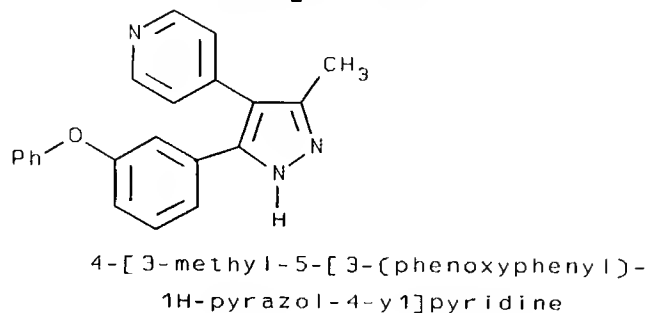
**Example A-12**

4-[5-[[1,1'-biphenyl]-4-yl]-3-methyl  
1H-pyrazol-4-yl]pyridine

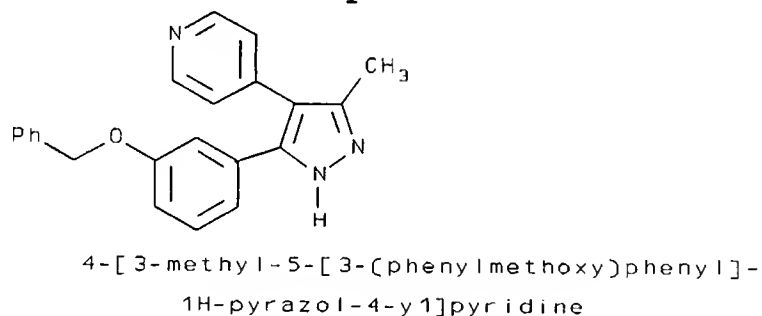
The same procedure as for the preparation of Example A-10 was used, substituting 4-formylbiphenyl in place of piperonal, to give 4-[5-[(1,1'-biphenyl)-4-yl]-3-methyl-

222

1H-pyrazol-4-yl]pyridine as a white solid: MS ( $M^+H$ ): 312 (base peak).

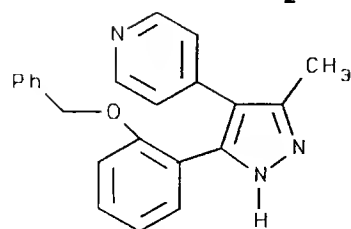
**Example A-13**

The same procedure for the preparation of Example A-10 was used, substituting 3-phenoxybenzaldehyde in place of piperonal, to give 4-[3-methyl-5-[3-(phenoxyphenyl)-1H-pyrazol-4-yl]pyridine as a white solid.

**Example A-14**

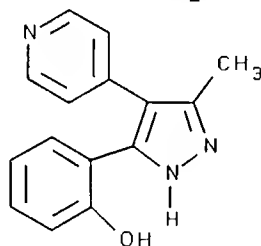
The same procedure for the preparation of Example A-10 was used, substituting 3-benzylmethoxybenzaldehyde in place of piperonal, to give 4-[3-methyl-5-[3-(benzylmethoxy)phenyl]-1H-pyrazol-4-yl]pyridine as a white solid: MS ( $M^+H$ ): 342 (base peak).

223

**Example A-15**

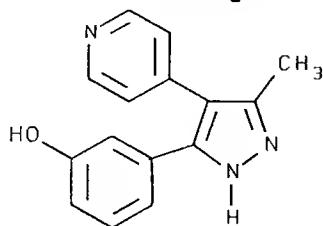
4-[3-methyl-5-[2-(phenylmethoxy)-  
phenyl]-1H-pyrazol-4-yl]pyridine

The same procedure for the preparation of Example A-10 was used, substituting 2-benzyloxybenzaldehyde in place of piperonal, to give 4-[3-methyl-5-[2-(phenylmethoxy)phenyl]-1H-pyrazol-4-yl]pyridine. MS ( $M^+H$ ): 342 (base peak).

**Example A-16**

2-[3-methyl-4-(4-pyridinyl)-1H-  
pyrazol-4-yl]phenol

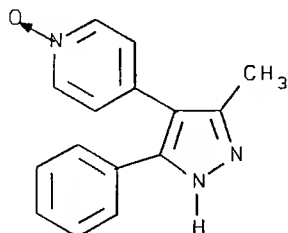
The same procedure for the preparation of Example A-10 was used, substituting 2-hydroxybenzaldehyde in place of piperonal, to give 2-[3-methyl-4-(4-pyridinyl)-1H-pyrazol-4-yl]phenol: MS ( $M^+H$ ): 252 (base peak).

**Example A-17**

3-[3-methyl-4-(4-pyridinyl)-1H-  
pyrazol-4-yl]phenol

The same procedure for the preparation of Example A-10 was used, substituting 3-hydroxybenzaldehyde in place of piperonal, to give 3-[3-methyl-4-(4-pyridinyl)-1H-pyrazol-4-yl]phenol: MS ( $M^+H$ ): 252 (base peak).

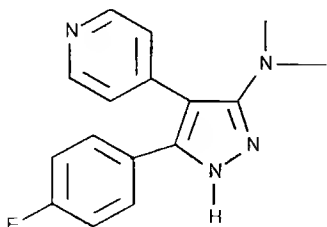
#### Example A-18



1-hydroxy-4-[3-methyl-5-phenyl-1H-pyrazol-4-yl]pyridinium

To a solution of 4-(3-methyl-5-phenyl-1H-pyrazol-4-yl)pyridine (Example A-2) (2.06 g, 8.76 mmol) in a mixture of  $\text{CH}_2\text{Cl}_2$  (10 mL) and MeOH (20 mL), was added 3-chloroperoxybenzoic acid (57~86%) (2.65 g, 8.76 mmol). The reaction was stirred at room temperature for 2h, quenched with  $\text{K}_2\text{CO}_3$  solution (25%, 15 mL), and concentrated. The resulting residue was partitioned between EtOAc (2.0 L) and  $\text{H}_2\text{O}$  (500 mL). The organic layer was separated, washed with  $\text{H}_2\text{O}$  (500 mL), dried over  $\text{MgSO}_4$ , filtered and concentrated to give 1-hydroxy-4-[3-methyl-5-phenyl-1H-pyrazol-4-yl]pyridinium (1.12 g, 54.5%): MS ( $M^+H$ ): 252 (base peak).

#### Example A-19



5-(4-fluorophenyl)-N,N-dimethyl-4-(4-pyridinyl)-1H-pyrazol-3-amine

Step 1: Preparation of 1-fluoro-4-(4'-pyridylacetyl)benzene

To a solution of sodium bis(trimethylsilyl)amide (200 mL, 1.0 M in THF) at 0 °C was added a solution of 4-picoline (18.6 g, 0.20 mol) in dry THF (200 mL) over 30 minutes. The reaction mixture was stirred at 0-10 °C for another 30 minutes, then was added to a solution of ethyl 4-fluorobenzoate (16.8 g, 0.10 mol) in dry THF (200 mL) at such a rate that the internal temperature didn't exceed 15 °C. After the addition, the resulting yellow suspension was stirred at room temperature for 3 hours. Water (600 mL) was added and the aqueous phase was extracted with ethyl acetate (3 X 200 mL). The combined organic layers were washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo to give 1-fluoro-4-(4'-pyridylacetyl)benzene (19.9 g, 92 %) as an oil which solidified upon standing: m.p.: 90-91 °C; Anal. Calc'd for C<sub>13</sub>H<sub>10</sub>FN: C, 72.55; H, 4.68; N, 6.51. Found: C, 72.07; H, 4.66; N, 6.62.

Step 2: Preparation of 1-fluoro-4-(4'-pyridylbromoacetyl)benzene

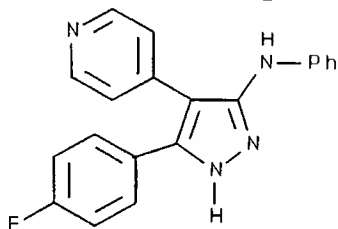
To a solution of 1-fluoro-4-(4'-pyridylacetyl)benzene (step 1) (10.0 g, 0.046 mol) in acetic acid (200 mL) was added a solution of bromine (8.2 g, 0.052 mol) in acetic acid (20 mL) dropwise. The reaction mixture was stirred at room temperature overnight. After the solvent was removed, the residue was triturated with ethyl acetate. A yellow solid formed, which was filtered and air-dried to give 1-fluoro-4-(4'-pyridylbromoacetyl)benzene (14.5 g). The compound was used in next step without further purification.



Step 3: Preparation of 5-(4-fluorophenyl)-N, N-dimethyl-4-(4-pyridinyl)-1H-pyrazol-3-amine

A mixture of 1-fluoro-4-(4'-pyridylbromoacetyl)-benzene (step 2) (3.8 g, 0.01 mol) and 4,4-dimethylamino-3-thiosemicarbazide (1.2 g, 0.01 mol) in ethanol (10 mL) was heated at reflux for 30 minutes. The dark green solution was cooled and poured into water (100 mL). The aqueous phase was extracted with methylene chloride (100 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated. The resulting residue was purified by chromatography (silica gel, ethyl acetate) to give 0.3 g 5-(4-fluorophenyl)-N, N-dimethyl-4-(4-pyridinyl)-1H-pyrazol-3-amine (0.3 g, 11 %) as a light yellow solid: m.p.: 245-247 °C. Anal. Calc'd for  $C_{16}H_{15}FN_4$ : C, 68.07; H, 5.36; N, 19.84. Found: C, 68.00; H, 5.37; N, 19.61.

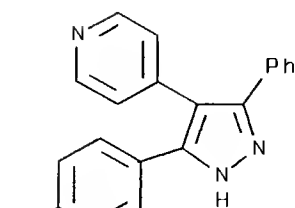
**Example A-20**



5-(4-fluorophenyl)-N-phenyl-4-(4-pyridinyl)-1H-pyrazol-3-amine

5-(4-Fluorophenyl)-N-phenyl-4-(4-pyridinyl)-1H-pyrazol-3-amine was prepared by the same procedure as described for Example A-19: m.p. 218-219 °C. Anal. Calc'd for  $C_{20}H_{15}FN_4 + 0.1 H_2O$ : C, 72.33; H, 4.61; N, 16.87. Found: C, 72.16; H, 4.56; N, 16.77.

## Example A-21



4-[5-(4-fluorophenyl)-3-phenyl-1H-pyrazol-4-yl]pyridine

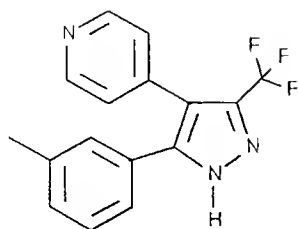
Step 1: Preparation of 1-fluoro-4-(4'-pyridylacetyl)benzene N-benzoylhydrazone

To a solution of benzoic hydrazide (1.36 g, 0.01 mol) in THF (20 mL) was added 1-fluoro-4-(4'-pyridylacetyl)benzene (2.15 g, 0.011 mol) in one portion followed by a drop of conc. HCl. The reaction mixture was stirred at room temperature overnight. There was white precipitate formed, which was filtered, washed with ether and air-dried to give 1-fluoro-4-(4'-pyridylacetyl)benzene N-benzoylhydrazone (2.90 g, 79 %) as a mixture of cis and trans (ratio, 1:9) isomers.

Step 2: Preparation of 4-[5-(4-fluorophenyl)-3-phenyl-1H-pyrazol-4-yl]pyridine

1-Fluoro-4-(4'-pyridylacetyl)benzene N-benzoylhydrazone (step 1) (0.50 g, 1.5 mmol) was heated at 180 °C under N<sub>2</sub> for 15 minutes, then cooled. The resulting solid was purified by chromatography (silica gel, 1:1 ethyl acetate/hexane) to give 4-[5-(4-fluorophenyl)-3-phenyl-1H-pyrazol-4-yl]pyridine (0.25 g, 53 %) as a pale yellow solid: m.p.: 265-267 °C. Anal. Calc'd for C<sub>20</sub>H<sub>14</sub>FN<sub>3</sub> + 0.25 H<sub>2</sub>O: C, 75.10; H, 4.57; N, 13.14. Found: C, 74.98; H, 4.49; N, 12.87.

228

**Example A-22**

4-[5-(3-methylphenyl)-3-(trifluoromethyl)-  
1H-pyrazol-4-yl]pyridine

Step 1: Preparation of 3-(4'-pyridylacetyl)toluene

3-(4'-Pyridylacetyl)toluene was prepared by the same method as described for Example A-19, step 1 in 70% yield.

Step 2: Preparation of trifluoroacetyl hydrazide

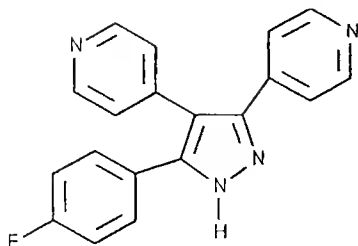
A mixture of ethyl trifluoroacetate (14.2 g, 0.10 mol) and hydrazine hydrate (5.54 g, 0.11 mol) in ethanol (25 mL) was heated at reflux for 6 hours. Solvent was removed and the resulting residue was dried in vacuum to give trifluoroacetyl hydrazide (12.3 g, 96 %) as a clear oil which solidified upon standing.

Step 3: Preparation of 4-[5-(3-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl]pyridine

A mixture of 3-(4'-pyridylacetyl)toluene (2.11 g, 0.01 mol) and trifluoroacetyl hydrazide (step 2) (1.0 g, 0.01 mol) was heated at 200 °C under N<sub>2</sub> for 15 minutes. The crude residue was purified by chromatography (silica gel, 35:65 ethyl acetate/hexane) to give 4-[5-(3-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl]pyridine (0.56 g) as a white solid: m.p. 237-239 °C. Anal. Calc'd for C<sub>16</sub>H<sub>12</sub>F<sub>3</sub>N<sub>3</sub>: C, 63.36; H, 3.99; N, 13.85. Found: C, 63.6; H, 4.00; N, 13.70.

229

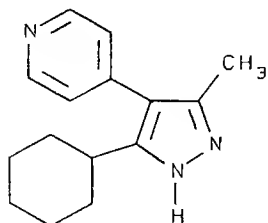
## Example A-23



4-[3-(4-fluorophenyl)-4-(4-pyridinyl)-  
1H-pyrazol-5-yl]pyridine

A mixture of 1-fluoro-4-(4'-pyridylacetyl)benzene (1.0 g, 4.6 mmol) and isonicotinic hydrazide (0.63 g, 4.6 mmol) in THF (25 mL) was heated to dissolution and then evaporated to dryness. The resulting solid was heated first to 140 °C, which caused a phase change, and subsequently melted on further heating until 180 °C whereupon a solid crystallized out. The reaction was immediately cooled, diluted with 10 % HCl (50 mL) and washed with chloroform. The aqueous layer was neutralized with bicarbonate and a tan colored solid was precipitated out. The solid was purified by treatment with activated carbon (Darco®) in boiling MeOH (100 mL), followed by filtration and concentration, to give 4-[3-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-5-yl]pyridine (1.05 g, 69 %) as a shiny tan solid: m.p. 304 °C (DSC). Mass (MH<sup>+</sup>) 137 (100%). Anal. Calc'd for C<sub>19</sub>H<sub>13</sub>N<sub>4</sub>F.1/4H<sub>2</sub>O: C, 71.13; H, 4.24; N, 17.46. Found: C, 70.88; H, 3.87; N, 17.38.

## Example A-24



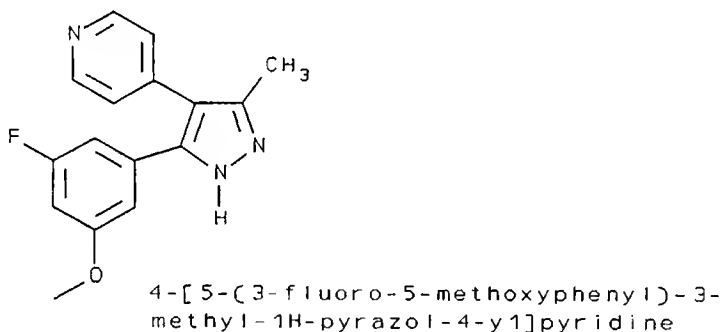
4-(5-cyclohexyl)-3-methyl-1H-pyrazol-4-yl]pyridine

Step 1: Preparation of 4-cyclohexyl-3-pyridyl-3-butene-2-one

4-Cyclohexyl-3-pyridyl-3-butene-2-one was prepared by the method of Example A-1, step 1 by replacing of 3-fluoro-*p*-anisaldehyde with cyclohexanecarboxaldehyde.

Step 2: Preparation of 4-(5-cyclohexyl)-3-methyl-1H-pyrazol-4-yl)pyridine

4-(5-Cyclohexyl)-3-methyl-1H-pyrazol-4-yl)pyridine was prepared by the method for Example A-1, step 2, by replacing 4-(3-fluoro-4-methoxyphenyl)-3-pyridyl-3-butene-2-one with 4-cyclohexyl-3-pyridyl-3-butene-2-one (step 1): Anal. Calc'd for C<sub>15</sub>H<sub>19</sub>N<sub>3</sub>: C, 73.56; H, 7.98; N, 17.16. Found: C, 73.72; H, 7.91; N, 19.98.

**Example A-25**

4-{5-(3-Fluoro-5-methoxyphenyl)-3-methyl-3-methyl-1H-pyrazol-4-yl}pyridine was prepared by the method of Example A-1, steps 1 and 2 by replacing 3-fluoro-*p*-anisaldehyde with 3-fluoro-*m*-anisaldehyde: Anal. Calc'd for C<sub>16</sub>H<sub>14</sub>N<sub>3</sub>OF: C, 67.83; H, 4.98; N, 14.83. Found: C, 67.68, H, 4.92; N, 14.92.

The following examples (No 26-55) listed in Table 1 were prepared by the procedures described above:

TABLE 1

No A-	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	m.p. or DSC(°C)	Anal. Calc'd Formula	Anal. Calc'd (calcd/found)		
							C	H	N
26	H				185-186	C <sub>18</sub> H <sub>19</sub> N <sub>3</sub>	77.95/ 77.51	6.90/ 6.93	15.15/ 14.73
27	H				142-144	C <sub>16</sub> H <sub>15</sub> N <sub>3</sub>	75.71/ 75.69	6.16/ 6.11	16.55/ 16.49
28	H				240-242	C <sub>22</sub> H <sub>19</sub> N <sub>3</sub> .0.25H <sub>2</sub> O	80.09/ 79.74	5.96/ 5.90	12.74/ 13.01
29	H				228.8	C <sub>16</sub> H <sub>12</sub> N <sub>3</sub> F <sub>3</sub>	63.36/ 63.28	3.99/ 3.73	13.85/ 13.69
30	H				189.6	C <sub>15</sub> H <sub>12</sub> N <sub>3</sub> Cl .0.15H <sub>2</sub> O	66.13/ 65.98	4.55/ 4.31	15.42/ 15.74
31	H				171.6	C <sub>17</sub> H <sub>17</sub> N <sub>3</sub> .0.2H <sub>2</sub> O	76.49/ 76.69	6.57/ 6.53	15.74/ 15.61
32					88.6	C <sub>16</sub> H <sub>14</sub> N <sub>3</sub> Cl	67.72/ 67.35	4.97/ 5.29	14.81/ 15.02
33	H				188.8	C <sub>16</sub> H <sub>14</sub> N <sub>3</sub> F	71.89/ 71.72	5.28/ 5.45	15.72/ 15.77
34	H				215.7	C <sub>17</sub> H <sub>17</sub> N <sub>3</sub>	77.54/ 77.24	6.51/ 6.80	15.96/ 15.71
35	H				201.4	C <sub>17</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub> .0.25H <sub>2</sub> O	68.10/ 67.92	5.88/ 5.65	14.01/ 13.65
36	H				210.7	C <sub>15</sub> H <sub>12</sub> N <sub>4</sub> O <sub>2</sub> .0.25H <sub>2</sub> O	63.26/ 63.59	4.42/ 4.39	19.67/ 19.31
37	H				252.5	C <sub>17</sub> H <sub>18</sub> N <sub>4</sub>	73.35/ 72.61	6.52/ 6.79	20.13/ 19.59
38	H				196.3	C <sub>17</sub> H <sub>15</sub> N <sub>3</sub> O	73.63/ 73.43	5.45/ 5.46	15.15/ 15.19
39	H				252.8	C <sub>15</sub> H <sub>12</sub> N <sub>3</sub> Br	57.34/ 57.09	3.85/ 3.79	13.37/ 13.06
40	H				198.5	C <sub>15</sub> H <sub>12</sub> N <sub>3</sub> F	71.13/ 71.23	4.78/ 5.01	16.59/ 16.76
41	H				225.6	C <sub>15</sub> H <sub>12</sub> N <sub>3</sub> F <sub>3</sub>	71.13/ 70.74	4.78/ 4.66	16.59/ 16.44
42	H				219.5	C <sub>16</sub> H <sub>12</sub> F <sub>3</sub> N <sub>3</sub>	63.36/ 63.19	3.99/ 4.07	13.85/ 13.38
43	H				227.7	C <sub>16</sub> H <sub>15</sub> N <sub>3</sub> .0.1H <sub>2</sub> O	76.53/ 76.53	6.10/ 6.20	16.73/ 16.49

232

No A-	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	m.p. or DSC(°C)	Anal. Calc'd Formula	Anal. Calc'd (calcd/found)		
							C	H	N
44	H				175.6	C <sub>16</sub> H <sub>15</sub> N <sub>3</sub> O .0.15H <sub>2</sub> O	71.70/ 71.92	5.75/ 5.76	15.68/ 15.29
45	H				—	C <sub>17</sub> H <sub>19</sub> N <sub>3</sub>	77.54/ 77.13	6.51/ 6.28	15.96/ 15.69
46	H				412.1	C <sub>15</sub> H <sub>11</sub> N <sub>3</sub> F <sub>2</sub>	66.42/ 66.12	4.09/ 3.86	15.49/ 15.25
47	H				168.5	C <sub>17</sub> H <sub>17</sub> N <sub>3</sub> O .0.15H <sub>2</sub> O	72.40/ 72.39	6.18/ 5.87	14.90/ 14.50
48	H				211.2	C <sub>16</sub> H <sub>12</sub> N <sub>3</sub> F <sub>3</sub> .0.2H <sub>2</sub> O	62.62/ 62.64	4.07/ 4.06	13.69/ 13.35
49	H				—	C <sub>13</sub> H <sub>11</sub> N <sub>3</sub> S	64.71/ 64.44	4.59/ 4.58	17.41/ 17.27
50	H				189.2	C <sub>15</sub> H <sub>11</sub> N <sub>3</sub> Cl <sub>2</sub>	59.23/ 59.22	3.65/ 3.24	13.81/ 13.81
51	H				211.7	C <sub>15</sub> H <sub>12</sub> N <sub>3</sub> Cl .0.15H <sub>2</sub> O	66.13/ 66.33	4.55/ 4.62	15.42/ 15.05
52	H				219.8	C <sub>16</sub> H <sub>14</sub> N <sub>3</sub> Cl	64.11/ 63.85	4.71/ 4.69	14.02/ 13.93
53	H				163.4	C <sub>19</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub> Cl	64.32/ 63.98	4.83/ 5.08	11.84/ 11.80
54				H	—	C <sub>15</sub> H <sub>12</sub> N <sub>3</sub> F .0.2H <sub>2</sub> O	70.15/ 70.18	4.86/ 4.60	16.35/ 16.47
55	H			H	—	C <sub>14</sub> H <sub>10</sub> N <sub>3</sub> F	70.28/ 69.97	4.21/ 3.84	17.56/ 17.53

The following pyrazoles could be prepared by the procedures described above:

Example A-56 5-[5-(3-chlorophenyl)-3-methyl-1H-pyrazol-4-yl]pyrimidin-2-amine;

Example A-57 5-[3-methyl-5-(3-methylphenyl)-1H-pyrazol-4-yl]pyrimidin-2-amine;

Example A-58 5-[3-methyl-5-(2-methylphenyl)-1H-pyrazol-4-yl]pyrimidin-2-amine;

Example A-59 5-[5-(4-chlorophenyl)-3-methyl-1H-pyrazol-4-yl]pyrimidin-2-amine;

Example A-60 5-[5-(4-fluorophenyl)-3-methyl-1H-pyrazol-4-yl]pyrimidin-2-amine;

Example A-61 5-[5-(4-methoxyphenyl)-3-methyl-1H-pyrazol-4-yl]pyrimidin-2-amine;

Example A-62 5-[5-(3-chlorophenyl)-3-methyl-1H-pyrazol-4-yl]pyridin-2-amine;

Example A-63 4-[5-(3-chlorophenyl)-3-methyl-1H-pyrazol-4-yl]pyridin-2-amine;

Example A-64 4-[5-(3-methylphenyl)-3-methyl-1H-pyrazol-4-yl]pyridin-2-amine;

Example A-65 4-[5-(2-methylphenyl)-3-methyl-1H-pyrazol-4-yl]pyridin-2-amine;

Example A-66 4-[5-(4-chlorophenyl)-3-methyl-1H-pyrazol-4-yl]pyridin-2-amine;

Example A-67 4-[5-(4-fluorophenyl)-3-methyl-1H-pyrazol-4-yl]pyridin-2-amine;

Example A-68 4-[5-(4-methoxyphenyl)-3-methyl-1H-pyrazol-4-yl]pyridin-2-amine;

Example A-69 5-[5-(3-chlorophenyl)-3-methyl-1H-pyrazol-4-yl]-2-methoxypyridine;

Example A-70 2-methoxy-5-[3-methyl-5-(3-methylphenyl)-1H-pyrazol-4-yl]pyridine;

Example A-71 2-methoxy-5-[5-(4-methoxyphenyl)-3-methyl-1H-pyrazol-4-yl]pyridine;

Example A-72 4-[5-(3-chlorophenyl)-3-methyl-1H-pyrazol-



4-yl]-2-methoxypyridine;

Example A-73 2-methoxy-4-[3-methyl-5-(3-methylphenyl)-1H-pyrazol-4-yl]pyridine;

Example A-74 2-methoxy-4-[3-methyl-5-(2-methylphenyl)-1H-pyrazol-4-yl]pyridine;

Example A-75 4-[5-(4-chlorophenyl)-3-methyl-1H-pyrazol-4-yl]-2-methoxypyridine;

Example A-76 4-[5-(4-fluorophenyl)-3-methyl-1H-pyrazol-4-yl]-2-methoxypyridine;

Example A-77 2-methoxy-4-[3-methyl-5-(4-methylphenyl)-1H-pyrazol-4-yl]pyridine;

Example A-78 5-[5-(3-chlorophenyl)-3-methyl-1H-pyrazol-4-yl]pyridin-2-ol;

Example A-79 4-[5-(3-chlorophenyl)-3-methyl-1H-pyrazol-4-yl]pyridin-2-ol;

Example A-80 4-[5-(3-methylphenyl)-3-methyl-1H-pyrazol-4-yl]pyridin-2-ol;

Example A-81 4-[5-(2-methylphenyl)-3-methyl-1H-pyrazol-4-yl]pyridin-2-ol;

Example A-82 4-[5-(4-chlorophenyl)-3-methyl-1H-pyrazol-4-yl]pyridin-2-ol;

Example A-83 4-[5-(4-fluorophenyl)-3-methyl-1H-pyrazol-4-yl]pyridin-2-ol;

Example A-84 4-[5-(4-methoxyphenyl)-3-methyl-1H-pyrazol-4-yl]pyridin-2-ol;

Example A-85 5-[5-(3-chlorophenyl)-3-methyl-1H-pyrazol-4-yl]pyridine-2-methanamine;

Example A-86 4-[5-(3-chlorophenyl)-3-methyl-1H-pyrazol-4-yl]pyridine-2-methanamine;

Example A-87 4-[5-(3-methylphenyl)-3-methyl-1H-pyrazol-4-yl]pyridine-2-methanamine;

Example A-88 4-[5-(2-methylphenyl)-3-methyl-1H-pyrazol-4-yl]pyridine-2-methanamine;

Example A-89 4-[5-(4-chlorophenyl)-3-methyl-1H-pyrazol-4-yl]pyridine-2-methanamine;

Example A-90 4-[5-(4-fluorophenyl)-3-methyl-1H-pyrazol-

4-yl]pyridine-2-methanamine;

Example A-91 4-[5-(4-methoxyphenyl)-3-methyl-1H-pyrazol-4-yl]pyridine-2-methanamine;

Example A-92 5-[5-(3-chlorophenyl)-3-methyl-1H-pyrazol-4-yl]pyridine-2-carboxamide;

Example A-93 4-[5-(3-chlorophenyl)-3-methyl-1H-pyrazol-4-yl]pyridine-2-carboxamide;

Example A-94 4-[5-(3-methylphenyl)-3-methyl-1H-pyrazol-4-yl]pyridine-2-carboxamide;

Example A-95 4-[5-(2-methylphenyl)-3-methyl-1H-pyrazol-4-yl]pyridine-2-carboxamide;

Example A-96 4-[5-(4-chlorophenyl)-3-methyl-1H-pyrazol-4-yl]pyridine-2-carboxamide;

Example A-97 4-[5-(4-fluorophenyl)-3-methyl-1H-pyrazol-4-yl]pyridine-2-carboxamide;

Example A-98 4-[5-(4-methoxyphenyl)-3-methyl-1H-pyrazol-4-yl]pyridine-2-carboxamide;

Example A-99 4-[5-(3-fluoro-4-methoxyphenyl)-3-methyl-1H-pyrazol-4-yl]pyridine;

Example A-100 4-[5-(4-fluoro-3-methoxyphenyl)-3-methyl-1H-pyrazol-4-yl]pyridine;

Example A-101 4-[5-(4-chloro-3-methoxyphenyl)-3-methyl-1H-pyrazol-4-yl]pyridine;

Example A-102 4-[5-(2,3-dihydrobenzofuran-6-yl)-3-methyl-1H-pyrazol-4-yl]pyridine;

Example A-103 4-[5-(benzofuran-6-yl)-3-methyl-1H-pyrazol-4-yl]pyridine;

Example A-104 4-[5-(3-fluoro-5-methoxyphenyl)-3-methyl-1H-pyrazol-4-yl]pyridine;

Example A-105 4-[5-(3-chloro-5-methoxyphenyl)-3-methyl-1H-pyrazol-4-yl]pyridine;

Example A-106 4-[5-(1-cyclohexyl-1-yl)-3-methyl-1H-pyrazol-4-yl]pyridine;

Example A-107 4-[5-(1,3-cyclohexadien-1-yl)-3-methyl-1H-pyrazol-4-yl]pyridine;

Example A-108 4-[5-(5,6-dihydro-2H-pyran-4-yl)-3-methyl-

1H-pyrazol-4-yl]pyridine;

Example A-109 4-(5-cyclohexyl-3-methyl-1H-pyrazol-4-yl)pyridine;

Example A-110 4-[5-(4-methoxy-3-methylphenyl)-3-methyl-1H-pyrazol-4-yl]pyridine;

Example A-111 4-[5-(3-methoxy-4-methylphenyl)-3-methyl-1H-pyrazol-4-yl]pyridine;

Example A-112 4-[5-(3-methoxy-5-methylphenyl)-3-methyl-1H-pyrazol-4-yl]pyridine;

Example A-113 4-[5-(3-furanyl)-3-methyl-1H-pyrazol-4-yl]pyridine;

Example A-114 2-methyl-4-(3-methyl-5-phenyl-1H-pyrazol-4-yl)pyridine;

Example A-115 2-methoxy-4-(3-methyl-5-phenyl-1H-pyrazol-4-yl)pyridine;

Example A-116 methyl 4-(3-methyl-5-phenyl-1H-pyrazol-4-yl)pyridine-2-carboxylate;

Example A-117 4-(3-methyl-5-phenyl-1H-pyrazol-4-yl)pyridine-2-carboxamide;

Example A-118 1-[4-(3-methyl-5-phenyl-1H-pyrazol-4-yl)pyridin-2-yl]ethanone;

Example A-119 N,N-dimethyl-4-(3-methyl-5-phenyl-1H-pyrazol-2-yl)pyridin-2-amine;

Example A-120 3-methyl-4-(3-methyl-5-phenyl-1H-pyrazol-4-yl)pyridine;

Example A-121 3-methoxy-4-(3-methyl-5-phenyl-1H-pyrazol-4-yl)pyridine;

Example A-122 methyl 4-(3-methyl-5-phenyl-1H-pyrazol-4-yl)pyridine-3-carboxylate;

Example A-123 4-(3-methyl-5-phenyl-1H-pyrazol-4-yl)pyridine-3-carboxamide;

Example A-124 1-[4-(3-methyl-5-phenyl-1H-pyrazol-4-yl)pyridin-3-yl]ethanone;

Example A-125 3-bromo-4-(3-methyl-5-phenyl-1H-pyrazol-4-yl)pyridine;

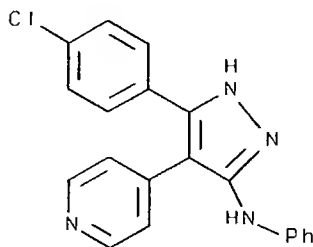
Example A-126 N,N-dimethyl-4-(3-methyl-5-phenyl-1H-

- pyrazol-2-yl)pyridin-3-amine;
- Example A-127 2-methyl-4-(3-methyl-5-phenyl-1H-pyrazol-4-yl)pyrimidine;
- Example A-128 4-(3-methyl-5-phenyl-1H-pyrazol-4-yl)pyrimidine;
- Example A-129 2-methoxy-4-(3-methyl-5-phenyl-1H-pyrazol-4-yl)pyrimidine;
- Example A-130 4-(3-methyl-5-phenyl-1H-pyrazol-4-yl)pyrimidin-2-amine;
- Example A-131 N,N-dimethyl-4-(3-methyl-5-phenyl-1H-pyrazol-4-yl)pyrimidin-2-amine;
- Example A-132 4-(5,6-dihydro-2H-pyran-4-yl)-3-methyl-5-phenyl-1H-pyrazole;
- Example A-133 3-methyl-5-phenyl-4-(3-thienyl)-1H-pyrazole;
- Example A-134 4-(3-furanyl)-3-methyl-5-phenyl-1H-pyrazole;
- Example A-135 3-methyl-5-phenyl-4-(2-thienyl)-1H-pyrazole;
- Example A-136 4-(2-furanyl)-3-methyl-5-phenyl-1H-pyrazole;
- Example A-137 4-(3-isothiazolyl)-3-methyl-5-phenyl-1H-pyrazole;
- Example A-138 4-(3-isoxazolyl)-3-methyl-5-phenyl-1H-pyrazole;
- Example A-139 4-(5-isothiazolyl)-3-methyl-5-phenyl-1H-pyrazole;
- Example A-140 4-(5-isoxazolyl)-3-methyl-5-phenyl-1H-pyrazole;
- Example A-141 3-methyl-5-phenyl-4-(5-thiazolyl)-1H-pyrazole;
- Example A-142 3-methyl-4-(5-oxazolyl)-5-phenyl-1H-pyrazole;
- Example A-143 2-methyl-4-[3-(3-methylphenyl)-1H-pyrazol-4-yl]pyridine;
- Example A-144 4-(1-methyl-3-phenyl-1H-pyrazol-4-

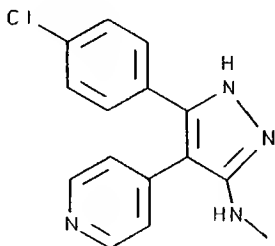
yl)pyridine;  
Example A-145 4-(3-phenyl-1H-pyrazol-4-yl)pyridine;  
Example A-146 2-methyl-4-(3-phenyl-1H-pyrazol-4-yl)pyridine;  
Example A-147 4-[3-(3-chlorophenyl)-1-methyl-pyrazol-4-yl]pyridine;  
Example A-148 4-[3-(4-chlorophenyl)-1-methyl-pyrazol-4-yl]pyridine;  
Example A-149 4-[3-(3-chlorophenyl)-1H-pyrazol-4-yl]pyridine;  
Example A-150 4-[3-(4-chlorophenyl)-1H-pyrazol-4-yl]pyridine;  
Example A-151 4-[3-(3-chlorophenyl)-1H-pyrazol-4-yl]-2-methylpyridine;  
Example A-152 4-[3-(3-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]pyridine;  
Example A-153 4-[3-(3-fluorophenyl)-1H-pyrazol-4-yl]pyridine; and  
Example A-154 4-[3-(3-chlorophenyl)-1-methyl-pyrazol-4-yl]-2-methylpyridine.

The compounds of Examples A-155 through A-172 were synthesized in accordance with the chemistry described above (particularly Scheme II) and illustrated by many of the previously disclosed Examples by selection of the corresponding starting reagents:

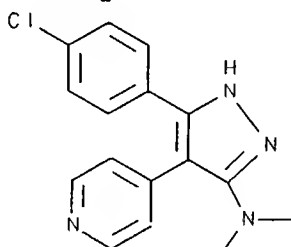
**Example A-155**



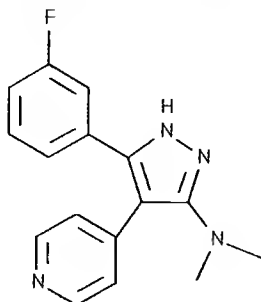
5-(4-chlorophenyl)-N-phenyl-4-(4-pyridinyl)-1H-pyrazol-3-amine: DSC 261 °C. Anal. Calc'd for  $C_{20}H_{15}ClN_4$  + 0.25  $H_2O$  (MW 351.32): C, 68.38, H, 4.30, N, 15.95. Found: C, 68.25, H, 4.41, N, 15.74.

**Example A-156**

5-(4-chlorophenyl)-N-methyl-4-(4-pyridinyl)-1H-pyrazol-3-amine: DSC 260 °C. Anal. Calc'd for  $C_{15}H_{13}ClN_4$  + 0.125  $H_2O$  (MW 287.00): C, 62.77, H, 4.57, N, 19.52. Found: C, 62.78, H, 4.33, N, 19.22.

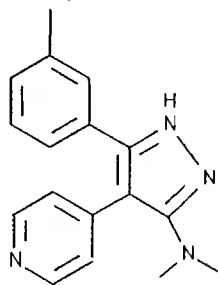
**Example A-157**

5-(4-chlorophenyl)-N,N-dimethyl-4-(4-pyridinyl)-1H-pyrazol-3-amine dihydrate: DSC 230 °C. Anal. Calc'd for  $C_{16}H_{15}ClN_4$  + 2  $H_2O$  (MW 334.81): C, 57.40, H, 4.52, N, 16.73. Found: C, 57.72, H, 4.85, N, 16.54.

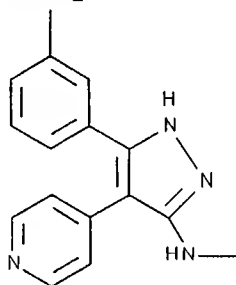
**Example A-158**

240

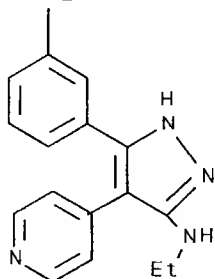
5-(3-fluorophenyl)-N,N-dimethyl-4-(4-pyridinyl)-1H-pyrazol-3-amine: DSC 227 °C. Anal. Calc'd for  $C_{16}H_{15}FN_4 + 0.125 H_2O$  (MW 284.57): C, 67.53, H, 5.31, N, 19.69. Found: C, 67.60, H, 5.20, N, 19.84.

**Example A-159**

N,N-dimethyl-5-(3-methylphenyl)-4-(4-pyridinyl)-1H-pyrazol-3-amine: DSC 222 °C. Anal. Calc'd for  $C_{17}H_{18}N_4 + 0.25 H_2O$  (MW 282.86): C, 72.19, H, 6.41, N, 19.81. Found: C, 71.99, H, 6.46, N, 19.90.

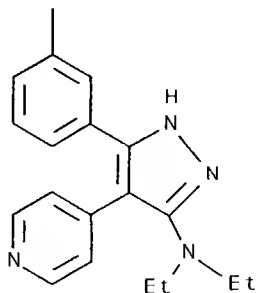
**Example A-160**

N-methyl-5-(3-methylphenyl)-4-(4-pyridinyl)-1H-pyrazol-3-amine: DSC 226 °C. Anal. Calc'd for  $C_{16}H_{16}N_4 + 0.125 H_2O$  (MW 266.58): C, 72.09, H, 6.05, N, 21.02. Found: C, 72.12, H, 6.12, N, 20.83.

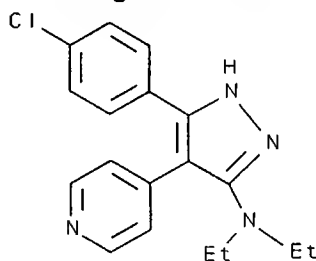
**Example A-161**

241

N-ethyl-5-(3-methylphenyl)-4-(4-pyridinyl)-1H-pyrazol-3-amine: DSC 227 °C. Anal. Calc'd for  $C_{17}H_{18}N_4 + 0.125 H_2O$  (MW 280.61): C, 72.77, H, 6.47, N, 19.97. Found: C, 72.63, H, 6.40, N, 19.73.

**Example A-162**

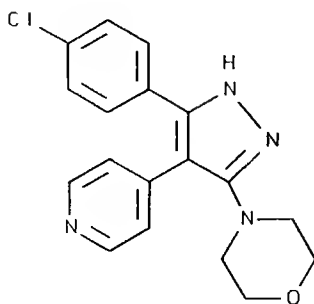
N,N-diethyl-5-(3-methylphenyl)-4-(4-pyridinyl)-1H-pyrazol-3-amine: DSC 234 °C. Anal. Calc'd for  $C_{19}H_{22}N_4$  (MW 306.41): C, 74.48, H, 7.24, N, 18.29. Found: C, 74.12, H, 7.18, N, 18.13.

**Example A-163**

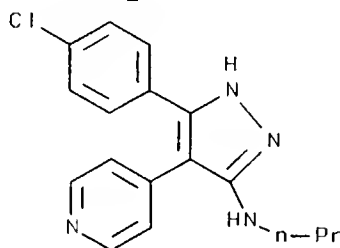
5-(4-chlorophenyl)-N,N-diethyl-4-(4-pyridinyl)-1H-pyrazol-3-amine: m.p. 260-261°C. Anal. Calc'd for  $C_{18}H_{19}ClN_4$  (MW 326.83): C, 66.15, H, 5.86, N, 17.14. Found: C, 66.03, H, 5.72, N, 17.23.^[



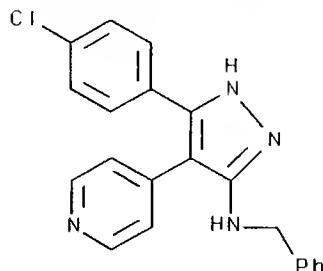
242

**Example A-164**

4-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]morpholine: DSC 279 °C. Anal. Calc'd for  $C_{18}H_{17}ClN_4O + 0.25 H_2O$  (MW 345.32): C, 62.61, H, 4.96, N, 16.23. Found: C, 62.52, H, 4.77, N, 16.52.

**Example A-165**

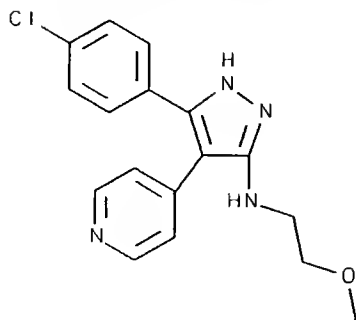
5-(4-chlorophenyl)-N-propyl-4-(4-pyridinyl)-1H-pyrazol-3-amine: DSC 244 °C. Anal. Calc'd for  $C_{17}H_{17}ClN_4 + 0.125 H_2O$  (MW 315.06): C, 64.81, H, 5.44, N, 17.78. Found: C, 64.94, H, 5.43, N, 17.78.

**Example A-166**

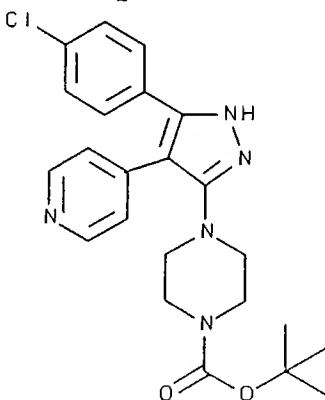
Isolated as 5-(4-chlorophenyl)-N-(phenylmethyl)-4-(4-pyridinyl)-1H-pyrazol-3-amine hydrate (2:1): DSC 237 °C. Anal. Calc'd for  $C_{21}H_{17}ClN_4 + 0.5 H_2O$  (MW 369.86): C, 68.20, H, 4.63, N, 15.15. Found: C, 68.09, H, 4.55, N,

243

15.15.

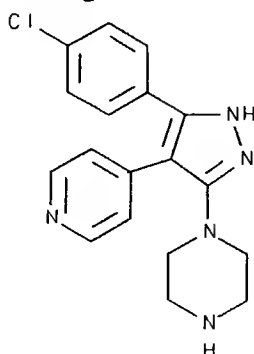
**Example A-167**

Isolated as 5-(4-chlorophenyl)-N-(2-methoxyethyl)-4-(4-pyridinyl)-1H-pyrazol-3-amine monohydrate: DSC 223 °C. Anal. Calc'd for  $C_{17}H_{17}ClN_4O + H_2O$  (MW 346.82): C, 58.87, H, 4.94, N, 16.15. Found: C, 58.59, H, 4.79, N, 16.02.

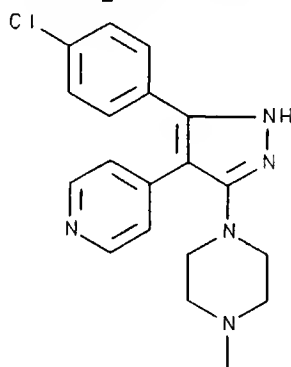
**Example A-168**

1,1-dimethylethyl 4-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1-piperazinecarboxylate: DSC 251 °C. Anal. Calc'd for  $C_{23}H_{26}ClN_5O$  (MW 439.95): C, 62.79, H, 5.96, N, 15.92. Found: C, 62.40, H, 5.82, N, 15.82.

244

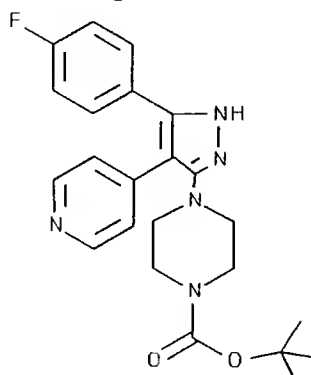
**Example A-169**

Isolated as 1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]piperazine trihydrochloride: DSC 99 °C. Anal. Calc'd for  $C_{18}H_{18}ClN_4 + 3 HCl$  (MW 449.21): C, 48.13, H, 4.71, N, 15.59. Found: C, 47.76, H, 5.07, N, 15.51.

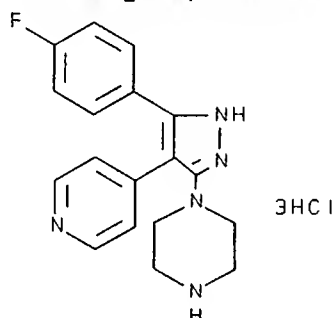
**Example A-170**

1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-methylpiperazine: m.p. 247-249 °C. Anal. Calc'd for  $C_{19}H_{20}ClN_5 + 0.75 H_2O$  (MW 367.33): C, 62.12, H, 5.49, N, 19.06. Found: C, 62.45, H, 5.86, N, 19.32.

245

**Example A-171**

1,1-dimethylethyl 4-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1-piperazinecarboxylate: m.p. 243-244 °C. Anal. Calc'd for  $C_{23}H_{26}FN_5O_2 + 0.5 CH_3CH_2CO_2CH_2CH_3$  (MW 467.55): C, 64.22, H, 6.47, N, 14.98. Found: C, 63.90, H, 6.41, N, 14.728.



1-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]piperazine trihydrochloride: m.p. 204-206 °C. Anal. Calc'd for  $C_{18}H_{18}FN_5 + 3 HCl + 0.5 H_2O$  (MW 441.77): C, 48.94, H, 4.79, N, 15.85. Found: C, 48.66, H, 4.88, N, 15.50.

1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]piperazine: m.p. 264-265 °C. Anal. Calc'd for  $C_{18}H_{18}ClN_5 + 0.125 H_2O$  (MW 342.08): C, 63.20, H, 5.30, N, 20.47. Found: C, 63.04, H, 5.36, N, 20.33.

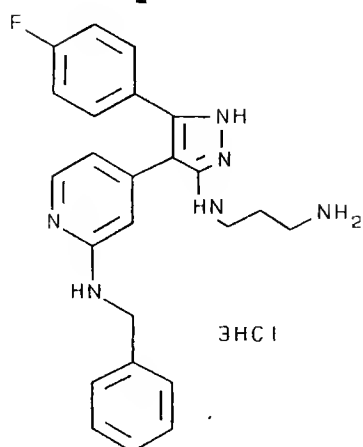
Additional compounds that were synthesized in accordance with the chemistry described in Scheme II by selection of the corresponding starting reagents further

include the compounds disclosed in Table 2.

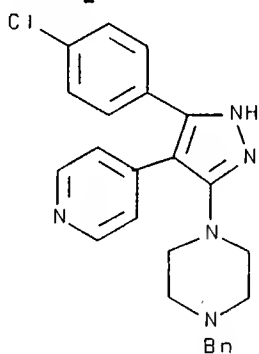
TABLE 2

Example	General	Formula	Microanalysis						DSC
			C calc	C found	H calc	H found	N calc	N found	
	<b>Procedure</b>								
A-173	Sch. II	C <sub>24</sub> H <sub>25</sub> ClN <sub>6</sub> •3HCl•1.5H <sub>2</sub> O	50.63	50.58	4.96	5.03	14.76	14.68	182
A-174	Sch. II	C <sub>25</sub> H <sub>24</sub> ClN <sub>5</sub> •0.125H <sub>2</sub> O	69.47	69.33	5.60	5.56	16.20	16.11	259
A-175	Sch. II	C <sub>17</sub> H <sub>17</sub> FN <sub>6</sub> •1.25H <sub>2</sub> O	48.64	48.45	4.56	4.86	20.02	20.24	82
A-176	Sch. II	C <sub>22</sub> H <sub>26</sub> ClN <sub>5</sub> O <sub>2</sub>	61.75	61.57	6.12	6.04	16.37	16.34	217
A-177	Sch. II	C <sub>17</sub> H <sub>18</sub> ClN <sub>5</sub> •3HCl•H <sub>2</sub> O	44.85	44.96	4.65	4.87	15.38	15.17	220
A-178	Sch. II	C <sub>21</sub> H <sub>24</sub> ClN <sub>5</sub> O <sub>2</sub> •0.125H <sub>2</sub> O	60.61	60.51	5.81	5.81	16.83	16.64	232
A-179	Sch. II	C <sub>25</sub> H <sub>30</sub> ClN <sub>5</sub> O <sub>3</sub>	62.04	61.76	6.25	6.25	14.47	14.37	220
A-180	Sch. II	C <sub>22</sub> H <sub>25</sub> FN <sub>6</sub> O <sub>2</sub> •0.5H <sub>2</sub> O	60.96	60.86	5.81	6.21	19.39	19.47	N.D.
A-181	Sch. II	C <sub>22</sub> H <sub>25</sub> ClFN <sub>5</sub> O <sub>2</sub>	59.26	58.98	5.65	5.55	15.71	15.36	210
A-182	Sch. II	C <sub>20</sub> H <sub>22</sub> ClN <sub>5</sub> •0.75H <sub>2</sub> O	62.98	62.97	5.81	5.64	18.36	17.83	271
A-183	Sch. II	C <sub>16</sub> H <sub>19</sub> Cl <sub>4</sub> N <sub>5</sub> •3HCl	45.41	45.37	4.53	4.74			120

248

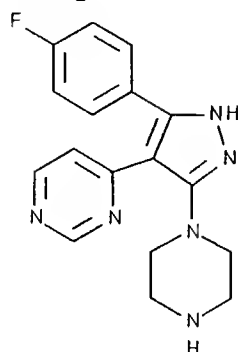
**Example A-173**

N-[5-(4-chlorophenyl)-4-[2-(phenylmethyl)amino]-4-pyridinyl]-1H-pyrazol-3-yl]-1,3-propanediamine, trihydrochloride

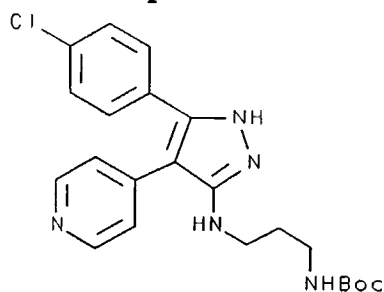
**Example A-174**

1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-(phenylmethyl)piperazine

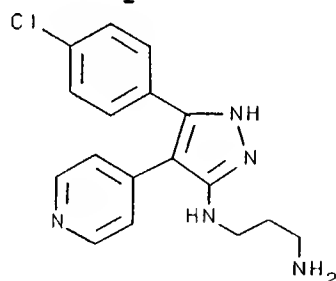
249

**Example A-175**

Isolated as 4-[3-(4-fluorophenyl)-5-(1-piperazinyl)-1H-pyrazol-4-yl]pyrimidine, dihydrochloride

**Example A-176**

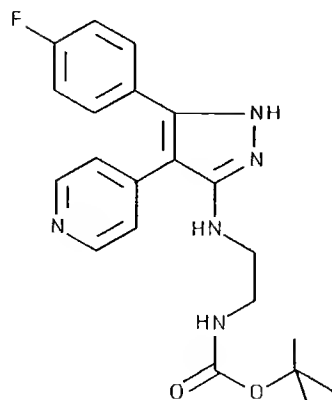
1,1-dimethylethyl [3-[[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]amino]propyl]carbamate

**Example A-177**

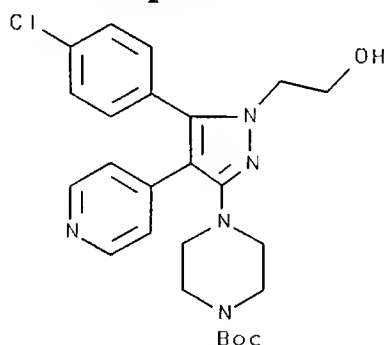
Isolated as N-[5-[4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1,3-propanediamine, trihydrochloride monohydrate



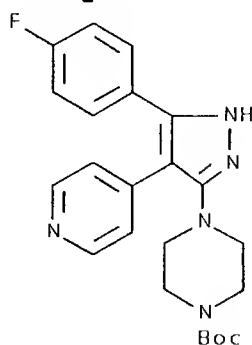
250

**Example A-178**

1,1-dimethylethyl [2-[[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]amino]ethyl]carbamate

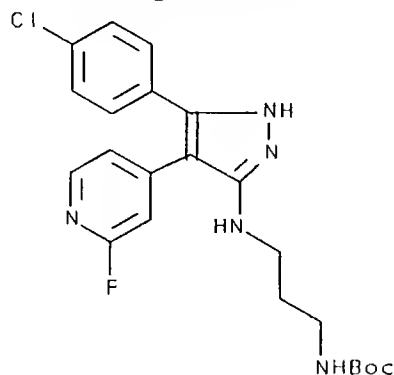
**Example A-179**

1,1-dimethylethyl 4-[5-(4-chlorophenyl)-1-(2-hydroxyethyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1-piperazinecarboxylate

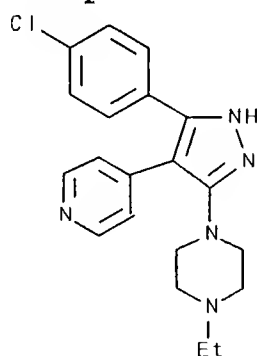
**Example A-180**

251

1,1-dimethylethyl 4-[5-(4-fluorophenyl)-4-(4-pyrimidinyl)-1H-pyrazol-3-yl]-1-piperazinecarboxylate

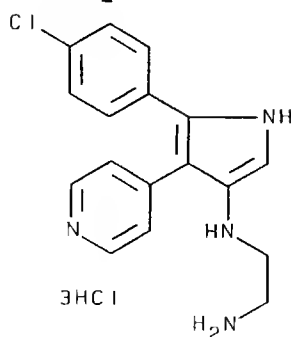
**Example A-181**

1,1-dimethylethyl [3-[[5-(4-chlorophenyl)-4-(2-fluoro-4-pyridinyl)-1H-pyrazol-3-yl]amino]propyl] carbamate

**Example A-182**

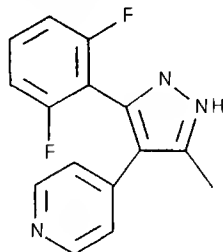
1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-ethylpiperazine

252

**Example A-183**

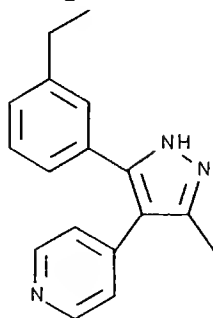
N-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1,2-ethanediamine

The compounds of Examples A-184 through A-189 were synthesized in accordance with the chemistry described above (particularly in Schemes I and IV) and illustrated by the previously disclosed Examples by selection of the corresponding starting reagents:

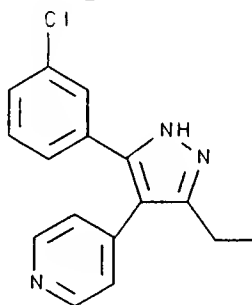
**Example A-184**

4-[3-(2,6-difluorophenyl)-5-methyl-1H-pyrazol-4-yl]pyridine: Anal. Calc'd for C<sub>15</sub>H<sub>11</sub>F<sub>2</sub>N<sub>3</sub>: C, 66.42; H, 4.09; N, 15.49. Found: C, 66.20; H, 3.94; N, 15.16; m.p. 236.67 °C.

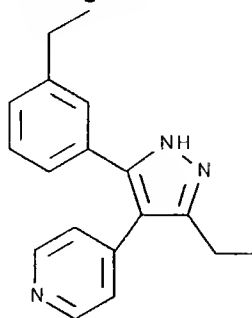
253

**Example A-185**

4-[3-(3-ethylphenyl)-5-methyl-1H-pyrazol-4-yl]pyridine: Anal. Calc'd for  $C_{17}H_{17}N_3$ : C, 77.54; H, 6.51; N, 15.96. Found; C, 77.16; H, 6.27; N, 15.69. m.p. (DSC): 189.25 °C.

**Example A-186**

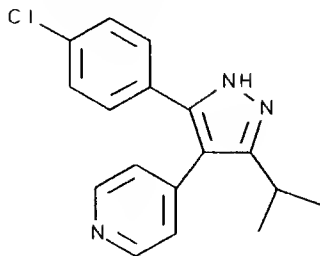
4-[3-(3-chlorophenyl)-5-ethyl-1H-pyrazol-4-yl]pyridine: Anal Calc'd for  $C_{16}H_{14}ClN_3 \cdot 0.1$  mole  $H_2O$ : C, 67.15; H, 4.91; N, 14.33. Found: C, 66.95; H, 5.00; N, 14.36. DSC: 176.18 °C.

**Example A-187**

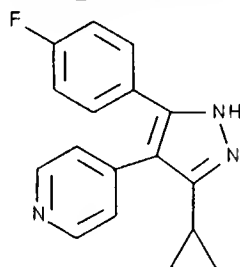
4-[3-ethyl-5-(3-ethylphenyl)-1H-pyrazol-4-yl]pyridine: Anal. Calc'd for  $C_{18}H_{19}N_3 \cdot 0.1$  mole  $H_2O$ : C,

254

77.44; H, 6.93; N, 15.05. Found: C, 77.39; H, 6.94; N, 14.93. m.p. (DSC): 192.66 °C.

**Example A-188**

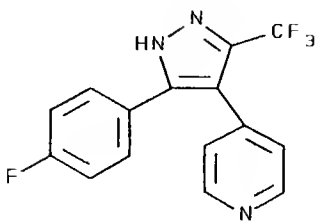
4-[3-(4-chlorophenyl)-5-(1-methylethyl)-1H-pyrazol-4-yl]pyridine: Anal. Calc'd for  $C_{17}H_{16}ClN_2 \cdot 0.4M$  EtOAc: C, 67.08; H, 5.81; N, 12.62. Found: C, 67.40; H, 6.15; N, 12.34.

**Example A-189**

4-[3-cyclopropyl-5-(4-fluorophenyl)-1H-pyrazol-4-yl]pyridine: Anal. Calc'd for  $C_{17}H_{14}FN_3$ : C, 73.1; H, 5.05; N, 15.04. Found: C, 73.23; H, 4.89; N, 14.63; m.p.: 239-240 °C.

The compound of Example A-190 was synthesized in accordance with the chemistry described above (particularly in Scheme III) and illustrated by the previously disclosed Examples by selection of the corresponding starting reagents:

255

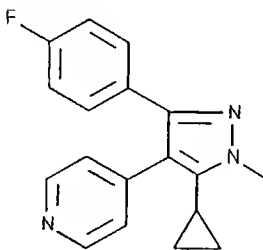
**Example A-190**

4-[3-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-4-yl]pyridine

This compound was prepared by the same procedure as described for Example A-22 by replacing 3-(4'-pyridylacetyl)toluene with 1-fluoro-4-(4'-pyridylacetyl)benzene (prepared as set forth in Example A-19).

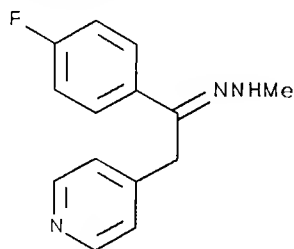
Anal. Calc'd for  $C_{15}H_9F_4N_3$ : C, 58.64; H, 2.95; N, 13.68. Found: C, 58.57; H, 3.07; N, 13.31. m.p. (DSC): 281.94 °C.

The compounds of Examples A-191 through A-198 were synthesized in accordance with the chemistry described above (particularly in Scheme V) by selection of the corresponding starting reagents:

**Example A-191**

4-[5-(cyclopropyl-3-(4-(fluorophenyl)-1-methyl-1H-pyrazol-4-yl)]pyridine

Step 1: Preparation of 1-(4-fluorophenyl)-2-(4-pyridinyl)ethanone methylhydrazone



1-(4-fluorophenyl)-2-(4-pyridinyl)ethanone methylhydrazone

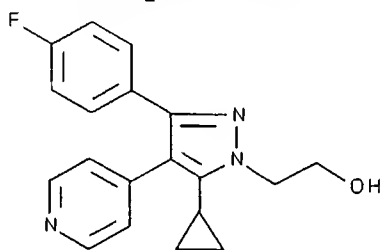
To a solution of 4-fluorobenzoyl-4'-pyridinyl methane (8.60 g, 0.04 mol) and methyl hydrazine (2.14 g, 0.044 mol) in 50 mL of ethanol was added two drops of concentrated sulfuric acid. The reaction mixture was stirred at room temperature overnight. After the removal of solvent, the residue was partitioned between ethyl acetate and water. The organic layer was washed with saturated sodium carbonate solution, washed with brine, and dried over magnesium sulfate. The filtrate was concentrated and the crude product was recrystallized from diethyl ether and hexane to afford 7.5 g of a yellow solid product (77% yield), 1-(4-fluorophenyl)-2-(4-pyridinyl)ethanone methylhydrazone.

Step 2: Preparation of 4-[5-(cyclopropyl-3-(4-(fluorophenyl)-1-methyl-1H-pyrazol-4-yl)]pyridine

To a solution of sodium hexamethyldisilazide (5.5 mL, 1.0 M in THF) at 0 °C was added a solution of the compound prepared in step 1 (0.67 g, 0.0028 mol) in 10 mL of dry THF dropwise. The dark brown solution was stirred at this temperature for 30 minutes. Then a solution of methyl cyclopropanecarboxylate (0.34 g, 0.0034 mol) in 5 mL of dry THF was added. The reaction mixture was allowed to warm up to room temperature and stirred for 3 hours. Water was added and the aqueous phase was extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and

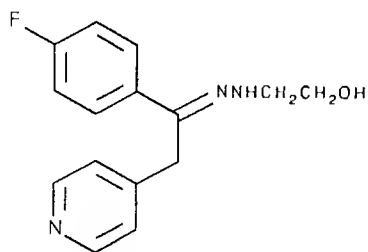
257

filtered. The filtrate was concentrated and purified by chromatography on silica gel (ethyl acetate/hexane/acetone, 10:9:1) to give 0.45 g of product, 4-[5-(cyclopropyl-3-(4-(fluorophenyl)-1-methyl-1H-pyrazol-4-yl)]pyridine, as a light yellow solid (55% yield), mp: 129-130 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.53 (m, 2H), 7.32 (m, 2H), 7.14 (m, 2H), 6.97 (m, 2H), 4.00 (s, 3H), 1.83 (m, 1H), 0.95 (m, 2H), 0.36 (m, 2H); Anal. Calc'd For C<sub>18</sub>H<sub>16</sub>FN<sub>3</sub>: C, 73.70; H, 5.50; N, 14.32. Found: C, 73.63; H, 5.57; N, 14.08.

**Example A-192**

5-cyclopropyl-3-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazole-1-ethanol

Step 1: Preparation of 1-(4-fluorophenyl)-2-(4-pyridinyl)ethanone (2-hydroxyethyl)hydrazone



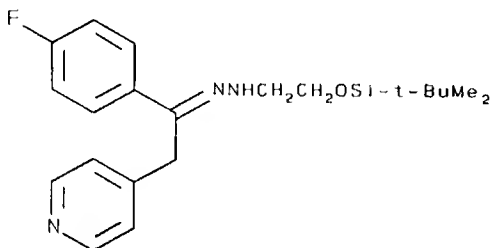
1-(4-fluorophenyl)-2-(4-pyridinyl)ethanone (2-hydroxyethyl)hydrazone

To a flask containing hydroxyethyl hydrazine (3.4 g, 0.04 mol) at 80 °C was added 4-fluorobenzoyl-4'-pyridinyl methane (8.6 g, 0.04 mol) portionwise. The yellow oil was stirred at this temperature overnight. The cooled



reaction mixture was dissolved with hot ethyl acetate and then triturated with hexane to give 8.9 g of product, 1-(4-fluorophenyl)-2-(4-pyridinyl)ethanone (2-hydroxyethyl)hydrazone, as a yellow crystal (81%), mp: 122-123 °C.

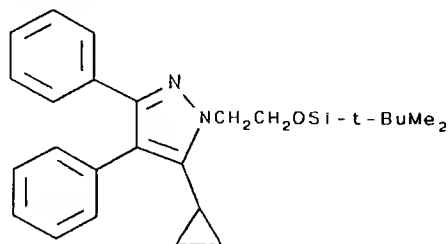
Step 2: Preparation of 1-(4-fluorophenyl)-2-(4-pyridinyl)ethanone [2-[[[1,1-dimethylethyl]dimethylsilyl]oxy]ethyl]hydrazone



1-(4-fluorophenyl)-2-(4-pyridinyl)ethanone  
[2-[[[1,1-dimethylethyl]dimethylsilyl]oxy]ethyl]hydrazone

To a solution of the 1-(4-fluorophenyl)-2-(4-pyridinyl)ethanone (2-hydroxyethyl)hydrazone prepared in step 1 (2.73 g, 0.01 mol) and (1,1-dimethylethyl)dimethylsilyl chloride (1.5 g, 0.01 mol) in 25 mL of DMF was added imidazole portionwise. The reaction mixture was stirred at room temperature overnight. Water was added and extracted with ethyl acetate, the organic layer was washed with water, washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated to give 3.8 g of crude product, 1-(4-fluorophenyl)-2-(4-pyridinyl)ethanone [2-[[[1,1-dimethylethyl]dimethylsilyl]oxy]ethyl]hydrazone, as a yellow oil that was used in the next step without further purification.

Step 3: 5-cyclopropyl-1-[2-[[[(1,1-dimethylethyl) dimethylsilyl]oxy]ethyl]-3,4-diphenyl-1H-pyrazole



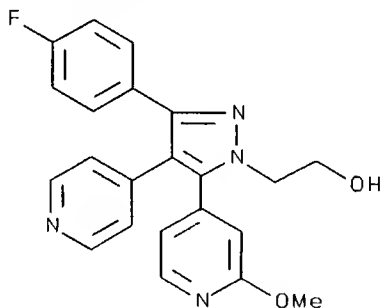
5-cyclopropyl-1-[2-[[[(1,1-dimethylethyl) dimethylsilyl]oxy]ethyl]-3,4-diphenyl-1H-pyrazole

To a solution of sodium hexamethyldisilazide (4.2 mL, 1.0 M in THF) at 0 °C was added a solution of the compound prepared in step 2 (0.78 g, 0.002 mol) in 10 mL of dry THF dropwise. The dark brown solution was stirred at this temperature for 30 minutes. Then a solution of methyl cyclopropanecarboxylate (0.27 g, 0.0026 mol) in 5 mL of dry THF was added. The reaction mixture was allowed to warm up to room temperature and stirred for 3 hours. Water was added and the aqueous phase was extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated and purified by chromatography on silica gel (ethyl acetate/hexane, 3:7) to give 0.30 g of product, 5-cyclopropyl-1-[2-[[[(1,1-dimethylethyl) dimethylsilyl]oxy]ethyl]-3,4-diphenyl-1H-pyrazole, as a light yellow oil (35% yield), <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.53 (m, 2H), 7.32 (m, 2H), 7.14 (d, *J* = 5.6 Hz, 2H), 6.97 (m, 2H), 4.47 (t, *J* = 4.8 Hz, 2H), 4.14 (t, *J* = 4.8 Hz, 2H), 1.93 (m, 1H), 0.95 (m, 2H), 0.87 (s, 9H), 0.41 (m, 2H); Anal. Calc'd For C<sub>25</sub>H<sub>32</sub>FN<sub>3</sub>OSi: C, 68.61; H, 7.37; N, 9.60. Found: C, 68.39; H, 7.81; N, 9.23.

Step 4: Preparation of 5-cyclopropyl-3-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazole-1-ethanol

To a solution of the compound prepared in step 3 (0.27 g, 0.00062 mol) in 5 mL of THF was added tetrabutylammonium fluoride (1.9 mL of 1.0 M THF solution) at room temperature. After 1 hour, water was added and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated and purified by chromatography on silica gel (ethyl acetate/hexane, 9:1) to give 0.16 g of product, 5-cyclopropyl-3-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazole-1-ethanol, as a pale yellow solid, mp: 155-157 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.53 (br s, 2H), 7.32 (m, 2H), 7.14 (d, *J* = 5.6 Hz, 2H), 6.97 (m, 2H), 4.42 (t, *J* = 4.8 Hz, 2H), 4.14 (t, *J* = 4.8 Hz, 2H), 1.83 (m, 1H), 0.93 (m, 2H), 0.35 (m, 2H); Anal. Calc'd For C<sub>19</sub>H<sub>18</sub>FN<sub>3</sub>O: C, 70.57; H, 5.61; N, 12.99. Found: C, 70.46; H, 5.87; N, 12.84.

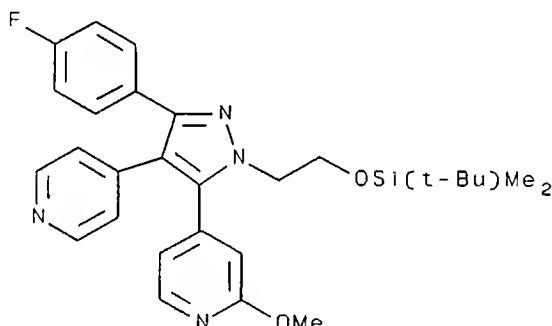
**Example A-193**



3-(4-fluorophenyl)-5-(2-methoxy-4-pyridinyl)-4-(4-pyridinyl)-1H-pyrazole-1-ethanol

To a solution of sodium hexamethyldisilazide (7.4 mL, 1.0 M in THF) at 0 °C was added a solution of the compound prepared in step 2 of Example A-192 (1.25 g, 0.0034 mol) in 15 mL of dry THF dropwise. The dark brown solution was stirred at this temperature for 30 minutes. Then a solution of methyl 4-(2-

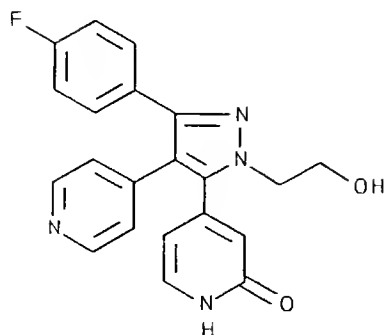
methoxy)pyridinecarboxylate (0.059 g, 0.0035 mol) in 5 mL of dry THF was added. The reaction mixture was allowed to warm up to room temperature and stirred for 3 hours. Water was added and the aqueous phase was extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated and purified by chromatography on silica gel (ethyl acetate/hexane, 1:1) to give 0.28 g of product, 3-(4-fluorophenyl)-5-(2-methoxy-4-pyridinyl)-4-(4-pyridinyl)-1H-pyrazole-1-ethanol, as a yellow solid, mp: 168-169 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.42 (m, 2H), 8.20 (dd, *J* = 0.7, 5.2 Hz, 1H), 7.37 (m, 2H), 7.02 (m, 2H), 6.95 (m, 2H), 6.71 (dd, *J* = 1.4, 5.2 Hz, 1H), 6.66 (t, *J* = 0.7 Hz, 1H), 4.20 (m, 2H), 4.14 (m, 2H), 3.95 (s, 3H); Anal. Calc'd for C<sub>22</sub>H<sub>19</sub>FN<sub>4</sub>O<sub>2</sub>: C, 67.86; H, 4.91; N, 14.35. Found: C, 67.46; H, 5.08; N, 14.03.



4-[1-[2-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]-3-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-5-yl]-2-methoxypyridine

A second compound, 4-[1-[2-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]-3-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-5-yl]-2-methoxypyridine also was isolated from the above reaction as a yellow oil by chromatography. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.45 (m, 2H), 8.20 (m, 1H), 7.40 (m, 2H), 7.04 (m, 2H), 6.93 (m, 2H), 6.81 (m, 2H), 4.24 (m, 2H), 4.14 (m, 2H), 3.98 (s, 3H), 0.83 (s, 9H), 0.02 (s, 6H).

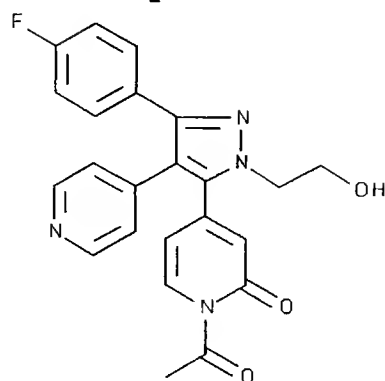
262

**Example A-194**

4-[3-(4-fluorophenyl)-1-(2-hydroxyethyl)-4-(4-pyridinyl)-1H-pyrazol-5-yl]-2(1H)-pyridinone

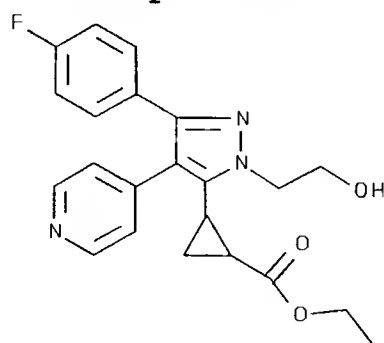
To a solution of 3-(4-fluorophenyl)-5-(2-methoxy-4-pyridinyl)-4-(4-pyridinyl)-1H-pyrazole-1-ethanol (0.28 g, 0.0006 mol) in 5 mL of acetic acid was added 3 mL of 48% hydrobromic acid. The reaction mixture was heated at reflux for 3 hour. The cooled mixture was then treated with water, basified with ammonium hydroxide and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated and purified by chromatography on silica gel (MeOH/CH<sub>2</sub>Cl<sub>2</sub>/NH<sub>4</sub>OH, 5:94:1) to give 0.07 g of product, 4-[3-(4-fluorophenyl)-1-(2-hydroxyethyl)-4-(4-pyridinyl)-1H-pyrazol-5-yl]-2(1H)-pyridinone, as a yellow solid (32% yield), mp: 250-251 °C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 11.74 (s, 1H), 8.45 (d, *J* = 5.0 Hz, 2H), 7.35 (m, 3H), 7.16 (m, 2H), 7.03 (d, *J* = 5.0 Hz, 2H), 6.37 (s, 1H), 6.05 (d, *J* = 5.2 Hz, 1H), 5.0 (m, 1H), 4.13 (m, 2H), 3.81 (m, 2H); Anal. Calc'd for C<sub>21</sub>H<sub>17</sub>FN<sub>4</sub>O<sub>2</sub>•0.2 H<sub>2</sub>O: C, 66.06; H, 4.65; N, 14.67. Found: C, 66.31; H, 4.49; N, 14.27.

263

**Example A-195**

1-acetyl-4-[3-(4-fluorophenyl)-1-(2-hydroxyethyl)-4-(4-pyridinyl)-1H-pyrazol-5-yl]-2(1H)-pyridinone

1-acetyl-4-[3-(4-fluorophenyl)-1-(2-hydroxyethyl)-4-(4-pyridinyl)-1H-pyrazol-5-yl]-2(1H)-pyridinone was obtained as a byproduct of the reaction of Example A-194 in the form of a yellow solid (38% yield), mp: 220-221 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.50 (m, 2H), 7.39 (m, 3H), 7.02 (m, 4H), 6.59 (m, 1H) 6.08 (dd,  $J$  = 1.4, 5.2 Hz, 1H), 4.52 (t,  $J$  = 6.0 Hz, 2H), 4.43 (t,  $J$  = 6.0 Hz, 2H), 2.04 (s, 3H); Anal. Calc'd for  $\text{C}_{23}\text{H}_{19}\text{FN}_4\text{O}_3 \cdot 0.3 \text{ H}_2\text{O}$ : C, 65.46; H, 4.63; N, 13.28. Found: C, 65.09; H, 4.64; N, 12.99.

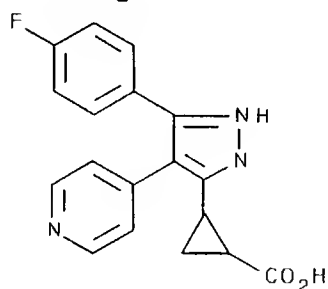
**Example A-196**

Ethyl 2-[3-(4-fluorophenyl)-1-(2-hydroxyethyl)-4-(4-pyridinyl)-1H-pyrazol-5-yl]cyclopropanecarboxylate

To a solution of sodium hexamethyldisilazide (17.0 mL, 1.0 M in THF) at 0 °C was added a solution of the

compound prepared in step 1 of Example A-192 (1.37 g, 0.005 mol) in 20 mL of dry THF dropwise. The dark brown solution was stirred at this temperature for 30 minutes. Then a solution of diethyl 1,2-cyclopropanedicarboxylate (1.12 g, 0.006 mol) in 10 mL of dry THF was added. The reaction mixture was allowed to warm up to room temperature and stirred for 2 hours. Water was added and the aqueous phase was extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated and purified by chromatography on silica gel (ethyl acetate/hexane, 8:2) to give 0.18 g of product, ethyl 2-[3-(4-fluorophenyl)-1-(2-hydroxyethyl)-4-(4-pyridinyl)-1H-pyrazol-5-yl]cyclopropanecarboxylate, as a light yellow oil (35% yield),  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.55 (m, 2H), 7.32 (m, 2H), 7.11 (m, 2H), 6.97 (m, 2H), 4.38 (m, 2H), 4.16 (m, 4H), 2.47 (m, 1H), 1.53 (m, 2H), 1.26 (t,  $J=7.0$  Hz, 3H), (m, 2H), 0.90 (m, 2H); Anal. Calc'd for  $\text{C}_{22}\text{H}_{22}\text{FN}_3\text{O}_3 \cdot 0.25 \text{H}_2\text{O}$ : C, 66.07; H, 5.67; N, 10.51 Found: C, 65.89; H, 5.80; N, 9.95.

#### Example A-197

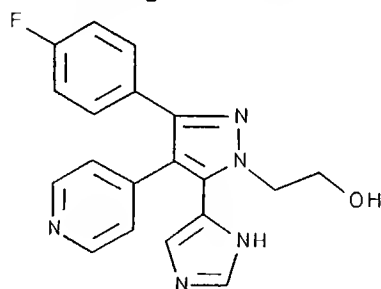


2-[3-(4-fluorophenyl)-1-(2-hydroxyethyl)-4-(4-pyridinyl)-1H-pyrazol-5-yl]cyclopropanecarboxylic acid

To a solution of ethyl 2-[3-(4-fluorophenyl)-1-(2-hydroxyethyl)-4-(4-pyridinyl)-1H-pyrazol-5-yl]cyclopropanecarboxylate prepared in accordance with Example A-196 (0.21 g, 0.00045 mol) in 10 mL of methanol

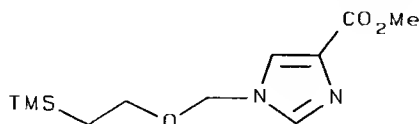
265

was added a solution of sodium hydroxide (0.09 g, 0.0022 mol) in 2 mL of water. The reaction mixture was stirred at reflux for 6 hours. After the solvent was removed, the residue was dissolved with 10 mL of 1N HCl and stirred for 30 minutes. The pH was then adjusted to 5-6 by addition of 1N sodium hydroxide solution and then extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium and filtered. The filtrate was concentrated and the crude was purified by recrystallization from ethanol and ether to give 0.1 g of product, 2-[3-(4-fluorophenyl)-1-(2-hydroxyethyl)-4-(4-pyridinyl)-1H-pyrazol-5-yl]cyclopropanecarboxylic acid, as a white solid (60% yield), mp: 253-255 °C; <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 8.46 (m, 2H), 7.32 (m, 2H), 7.25 (m, 2H), 7.04 (m, 2H), 4.39 (t, *J* = 5.0 Hz, 2H), 4.03 (m, 2H), 2.60 (m, 1H), 1.51 (m, 2H), 0.97 (m, 2H); Anal. Calc'd For C<sub>20</sub>H<sub>18</sub>FN<sub>3</sub>O<sub>3</sub>: C, 65.39; H, 4.94; N, 11.44. Found: C, 64.92; H, 4.77; N, 11.20.

**Example A-198**

3-(4-fluorophenyl)-5-(4-imidazolyl)-4-(4-pyridinyl)-1H-pyrazole-1-ethanol

Step 1: Preparation of methyl 1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrrole-3-carboxylate

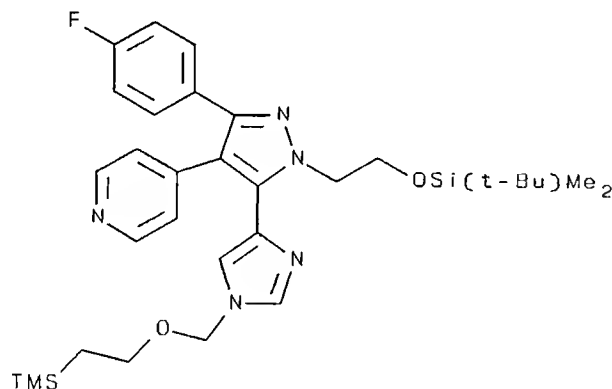




methyl 1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrrole-3-carboxylate

To a suspension of sodium hydride (1.0 g, 0.025 mol) in 50 mL of DMF was added methyl 4-imidazolecarboxylate (2.95 g, 0.023 mol) portionwise at room temperature. The mixture was stirred at room temperature for 0.5 hours. Then SEM-Cl (4.17 g, 0.025 mol) was added dropwise over 5 minutes. The reaction mixture was stirred for 4 hours and quenched by adding water. The aqueous phase was extracted with ethyl acetate and the organic layer was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated and the crude was purified by chromatography on silica gel (ethyl acetate/hexane, 8:2) to give 4.0 g of the major regioisomer as a clear oil.

Step 2: Preparation of 4-[1-[2-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]-3-(4-fluorophenyl)-5-[1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-imidazol-4-yl]-1H-pyrazol-4-yl]pyridine



4-[1-[2[[[(1,1-dimethylethyl)dimethylsilyl]-oxy]ethyl]-3-(4-fluorophenyl)-5-[1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-imidazol-4-yl]-1H-pyrazol-4-yl]pyridine

To a solution of sodium hexamethyldisilazide (4.5 mL, 1.0 M in THF) at 0 °C under Ar was added a solution of the compound prepared in step 2 of Example A-192 (0.8

g, 0.002 mol) in 10 mL of dry THF dropwise. The dark brown solution was stirred at this temperature for 30 minutes. Then a solution of the compound prepared in step 1 of the present Example (0.54 g, 0.0021 mol) in 5 mL of dry THF was added. The reaction mixture was allowed to warm up to room temperature and stirred for 1 hour. Water was added and the aqueous phase was extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated and purified by chromatography on silica gel (ethyl acetate/hexane, 8:2) to give 0.98 g of product as a light yellow oil which solidified upon standing (91% yield), mp: 79-80 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.48 (d, *J* = 6.0 Hz, 2H), 7.68 (d, *J* = 1.3 Hz, 1H), 7.38 (d, *J* = 6.0 Hz, 2H), 7.10 (m, 2H), 7.00 (m, 2H), 6.93 (d, *J* = 1.3 Hz, 1H), 5.25 (s, 2H), 4.53 (t, *J* = 6.0 Hz, 2H), 4.12 (t, *J* = 6.0 Hz, 2H), 3.84 (t, *J* = 8.0 Hz, 2H), 0.92 (t, *J* = 8.0 Hz, 2H), 0.84 (s, 9H), 0.021 (s, 18H); Anal. Calc'd For C<sub>31</sub>H<sub>44</sub>FN<sub>5</sub>O<sub>2</sub>Si<sub>2</sub>: C, 62.70; H, 7.47; N, 11.79. Found: C, 62.98; H, 7.74; N, 11.88.

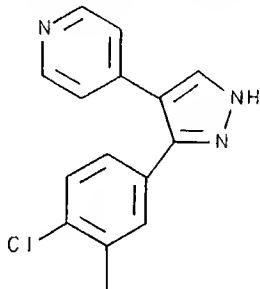
Step 3: Preparation of 3-(4-fluorophenyl)-5-(4-imidazolyl)-4-(4-pyridinyl)-1H-pyrazole-1-ethanol

To a solution of the compound prepared in step 2 of the present Example (0.54 g, 0.001 mol) in 10 mL of THF was added a solution of tetrabutylammonium fluoride (1.0 M in THF). After the mixture was heated at reflux for 3 hours, the solvent was removed and the residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated and the crude product was purified on silica gel (methylene chloride/methanol, 95:5) to give 0.22 g of the product, 3-(4-fluorophenyl)-5-(4-imidazolyl)-4-(4-pyridinyl)-1H-pyrazole-1-ethanol, as a white solid (63% yield), mp: 227-228 °C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 8.45 (m, 2H), 7.83 (s,

268

1H), 7.35 (m, 2H), 7.15 (m, 4H), 7.09 (s, 1H), 5.20 (br s, 1H), 4.32 (s, 2H), 3.81 (m, 2H); Anal. Calc'd For  $C_{19}H_{16}FN_5O$ : C, 65.32; H, 4.62; N, 20.05. Found: C, 64.98; H, 4.55; N, 19.79.

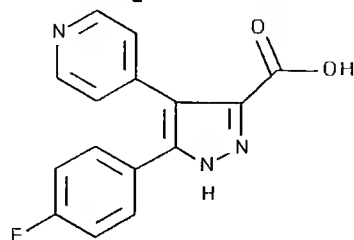
The compound of Example A-199 was synthesized in accordance with the chemistry described above (particularly in Scheme VI) by selection of the corresponding starting reagents:

**Example A-199**

4-[3-(4-chloro-3-methylphenyl)-1H-pyrazol-4-yl]pyridine

Anal. Calc'd for  $C_{15}H_{12}N_3Cl$  (269.74): C, 66.79; H, 4.48; N, 15.58. Found: C, 66.57; H, 4.15; N, 15.54. m.p. (DSC): 198.17 °C.

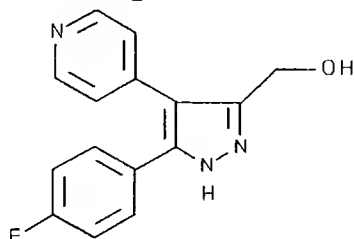
The compounds of Examples A-200 through A-202 were synthesized in accordance with the chemistry described above (particularly in Scheme VII) by selection of the corresponding starting reagents:

**Example A-200**

5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazole-3-carboxylic acid

A mixture of 4-[3-(4-fluorophenyl)-5-methyl-1H-pyrazol-4-yl]pyridine prepared as set forth in Example A-4 (5.83 g, 24.0909 mmol) and potassium permanganate (7.6916 g, 48.1818 mmol) in water (7.5 ml) and tert-butanol (10 ml) was heated at reflux for 6 hours (or until all the potassium permanganate was consumed). The mixture was then stirred at room temperature overnight and then diluted with water (150 ml). Manganese dioxide was removed from the mixture by filtration. The filtrate was extracted with ethyl acetate to remove unreacted starting material. The aqueous layer was acidified with 1N HCl to increase the pH to about 6. A white precipitate formed, was collected by filtration, washed with water, and dried in a vacuum oven to give 5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazole-3-carboxylic acid (isolated as the monohydrate salt) (2.9777 g, 43.7 %). Anal. Calc'd for  $C_{15}H_{10}N_3FO_2 \cdot H_2O$  (283 + 18): C, 59.80; H, 4.01; N, 13.95; Found: C, 59.48; H, 3.26; N, 13.65. MS ( $MH^+$ ): 284 (base peak).

**Example A-201**

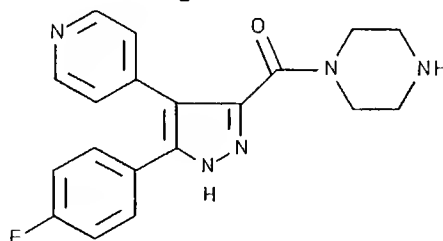


5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazole-3-methanol

To a suspension of 5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazole-3-carboxylic acid, monohydrate prepared in accordance with Example A-200 (0.526 g, 2.0 mmol) in dry THF (15 ml) at reflux under nitrogen, a

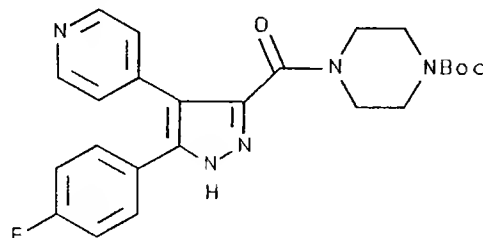
270

solution of 1N lithium aluminum hydride in THF (4.0 ml, 4.0 mmol) was added dropwise over 15 minutes. A precipitate formed. The mixture was boiled for an additional hour. Excess lithium aluminum hydride was then decomposed by cautiously adding a solution of 4N potassium hydroxide in water (0.5 ml). Upon hydrolysis, a white salt precipitated. After the addition was complete, the mixture was heated at reflux for 15 minutes. The hot solution was filtered by suction through a Buchner funnel, and remaining product was extracted from the precipitate by refluxing with THF (15 ml) for 1 hour, followed again by suction filtration. The combined filtrates were concentrated under reduced pressure. The resulting residue was taken into ethyl acetate, washed with water and brine, dried over  $\text{MgSO}_4$  to give a crude product (0.45 g). Recrystallization of the crude product from methanol gave 5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazole-3-methanol (0.2808 g, 56.5%). DSC: 260.26 °C; Anal. Calc'd for  $\text{C}_{15}\text{H}_{12}\text{N}_3\text{FO}$  (269): C, 66.91; H, 4.49; N, 15.60; Found: C, 66.07; H, 4.63; N, 15.20. MS ( $\text{MH}^+$ ): 270 (base peak).

**Example A-202**

1-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]carbonyl]piperazine

Step 1: Preparation of 1,1-dimethylethyl 4-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]carbonyl]-1-piperazinecarboxylate



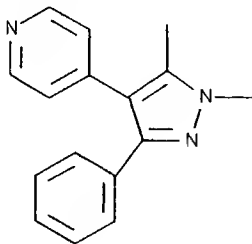
To a solution of 5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazole-3-carboxylic acid, monohydrate prepared in accordance with Example A-200 (0.9905 g, 3.5 mmol) and 1-hydroxybenzotriazole (0.4824 g, 3.57 mmol) in DMF (20 ml) at 0 °C under nitrogen, 1-(3-dimethylaminopropyl)3-ethylcarbodiimide hydrochloride (0.6984 g, 3.57 mmol, Aldrich Chemical Co.) was added. The solution was stirred at 0 °C under nitrogen for 1 hour then 1-butoxycarbonylpiperazine (0.6585 g, 3.5 mmol) was added followed by N-methylmorpholine (0.40 ml, 3.6 mmol). The reaction was stirred from 0 °C to room temperature overnight. After 19 hours, the solvent was removed under reduced pressure, and resulting residue was diluted with ethyl acetate, washed with saturated NaHCO<sub>3</sub> solution, water and brine, and dried over MgSO<sub>4</sub>. After filtration, the solvent was removed under reduced pressure to give a crude product (1.7595 g). 1,1-Dimethylethyl 4-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]carbonyl]-1-piperazinecarboxylate (1.2372 g, 78.4%) was obtained by chromatography. Anal. Calc'd for C<sub>24</sub>H<sub>26</sub>N<sub>5</sub>O<sub>3</sub>F. (451): C, 63.85; H, 5.80; N, 15.51; Found: C, 63.75; H, 5.71; N, 15.16. MS (MH<sup>+</sup>): 452 (base peak).

Step 2: Preparation of 1-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]carbonyl]piperazine bis(trifluoroacetate), monohydrate

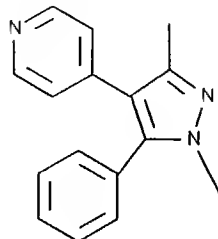
A solution of the compound prepared in step 1 (0.1804 g, 0.4 mmol) in methylene chloride (1.0 ml) and TFA (0.3 ml) was stirred at room temperature under nitrogen for 2 hours. The solvent was removed under reduced pressure and TFA was chased by methylene chloride and methanol. The resulting colorless oily residue was dried in a vacuum oven overnight to give 1-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]carbonyl]piperazine (isolated as the bis(trifluoroacetate), monohydrate salt) (0.2400g, 100%) as a white solid. Anal. Calc'd for  $C_{19}H_{18}N_5OF \cdot 2CF_3COOH \cdot H_2O$  (351 + 228 + 18): C, 46.24; H, 3.71; N, 11.72; Found: C, 45.87; H, 3.43; N, 11.45. MS ( $MH^+$ ): 352 (base peak).

The compounds of Examples A-203 through A-206 were synthesized in accordance with the chemistry described above (particularly in Scheme VIII) by selection of the corresponding starting reagents:

**Example A-203**



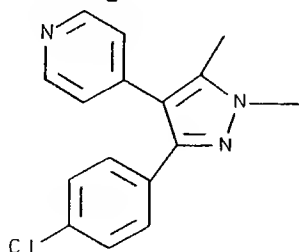
4-(1,5-dimethyl-3-phenyl-1H-pyrazol-4-yl)pyridine



## 4-(1,3-dimethyl-5-phenyl-1H-pyrazol-4-yl)pyridine

A 60% dispersion of sodium hydride (41 mg, 0.00172 moles) (prewashed with hexane) in mineral oil (69 mg) was added with 5 ml of dioxane to a stirred solution of 4-(3-methyl-5-phenyl-1H-pyrazol-4-yl)pyridine (200 mg, 0.00086 moles) (prepared as set forth in Example A-2) in 50 ml of dioxane. After 3 hours a solution of  $\text{CH}_3\text{I}$  (122 mg, 0.00086 mole) in 10 ml dioxane was added and the mixture was stirred at room temperature for 20 hours. The mixture was concentrated to a solid. The products were partitioned between water (15 ml) and ethyl acetate (50 ml). The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to a solid. The products were purified and separated by radial chromatography. NMR (NOE experiments) showed that the first component off the column (the minor component) was 4-(1,3-dimethyl-5-phenyl-1H-pyrazol-4-yl)pyridine, and the second material off the column was 4-(1,5-dimethyl-3-phenyl-1H-pyrazol-4-yl)pyridine.

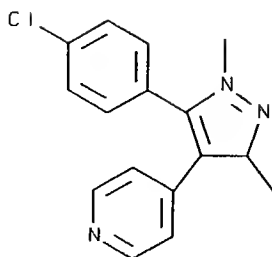
Major isomer (4-(1,5-dimethyl-3-phenyl-1H-pyrazol-4-yl)pyridine): m.p.: 94-99 °C. Anal. calc'd for  $\text{C}_{16}\text{H}_{15}\text{N}_3 \cdot 0.1\text{MH}_2\text{O}$ : C, 77.08; H, 6.06; N, 16.85. Found: C, 76.59; H, 5.70; N, 16.62

**Example A-204**

4-[3-(4-chlorophenyl)-1,5-dimethyl-1H-pyrazol-4-yl]pyridine



274



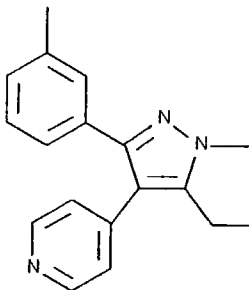
4-[5-(4-chlorophenyl)-1,3-dimethyl-1H-pyrazol-4-yl]pyridine (the compound of Example A-32)

4-[3-(4-chlorophenyl)-1,5-dimethyl-1H-pyrazol-4-yl]pyridine and 4-[5-(4-chlorophenyl)-1,3-dimethyl-1H-pyrazol-4-yl]pyridine were prepared by the same procedure as described for Example A-203 by replacing 4-(3-methyl-5-phenyl-1H-pyrazol-4-yl)pyridine with 4-(3-(4-chlorophenyl)-5-methyl-1H-pyrazol-4-yl)pyridine (prepared as set forth in Example A-7).

Major Isomer (4-[3-(4-chlorophenyl)-1,5-dimethyl-1H-pyrazol-4-yl]pyridine): Anal. calc'd for  $C_{16}H_{14}N_3Cl$  (283.76): C, 67.72; H, 4.97; N, 14.81; Found: C, 67.45; H, 4.71; N, 14.63. m.p. (DSC): 190.67 °C.

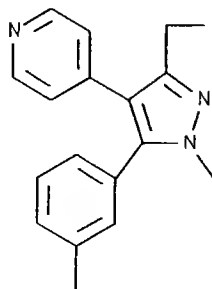
Minor Isomer (4-[5-(4-chlorophenyl)-1,3-dimethyl-1H-pyrazol-4-yl]pyridine): m.p.: 82-88 °C. Anal. calc'd for  $C_{16}H_{14}N_3Cl$ : C, 67.72; H, 4.97; N, 14.81; Found: C, 67.56; H, 4.96; N, 14.73.

#### Example A-205



275

4-[5-ethyl-1-methyl-3-(3-methylphenyl)-1H-pyrazol-4-yl]pyridine



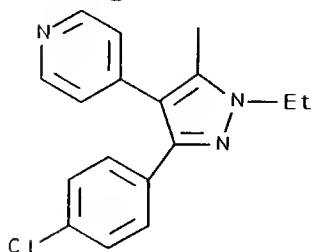
4-[3-ethyl-1-methyl-5-(3-methylphenyl)-1H-pyrazol-4-yl]pyridine

4-[5-ethyl-1-methyl-3-(3-methylphenyl)-1H-pyrazol-4-yl]pyridine and 4-[3-ethyl-1-methyl-5-(3-methylphenyl)-1H-pyrazol-4-yl]pyridine were prepared by the same procedure as described for Example A-203 by replacing 4-(3-methyl-5-phenyl-1H-pyrazol-4-yl)pyridine with 4-(3-(4-methylphenyl)-5-ethyl-1H-pyrazol-4-yl)pyridine (prepared as set forth in Example A-45).

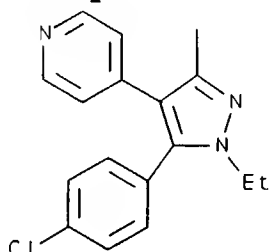
Major Isomer (4-[5-ethyl-1-methyl-3-(3-methylphenyl)-1H-pyrazol-4-yl]pyridine): Anal. Calc'd for  $C_{18}H_{19}NO_3 \cdot 0.45$   $MH_2O$ : C, 75.73; H, 7.03; N, 14.77. Found: C, 76.03; H, 6.87; N, 14.28.

Minor Isomer (4-[3-ethyl-1-methyl-5-(3-methylphenyl)-1H-pyrazol-4-yl]pyridine): Anal. Calc'd for  $C_{18}H_{19}NO_3 \cdot 0.30$   $MH_2O$ : C, 76.46; H, 6.99; N, 14.86. Found: C, 76.58; H, 6.98; N, 14.63.

276

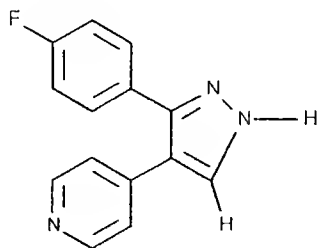
**Example A-206**

4-[3-(4-chlorophenyl)-1-ethyl-5-methyl-1H-pyrazol-4-yl]pyridine: Anal. Calc'd for  $C_{17}H_{16}N_3Cl$  (297.79): C, 68.57; H, 5.42; N, 14.11. Found: C, 68.33; H, 5.27; N, 14.08; m.p. (DSC) 164.36 °C.

**Example A-207**

4-[3-(4-chlorophenyl)-2-ethyl-5-methyl-1H-pyrazol-4-yl]pyridine: Anal. Calc'd for  $C_{17}H_{16}N_3Cl$  (297.79): C, 68.57; H, 5.42; N, 14.11. Found: C, 68.25; H, 5.36; N, 13.74; m.p. (DSC) 153.46 °C.

The compounds of Examples A-208 and A-209 were prepared in accordance with the chemistry described above (particularly in Scheme IX):

**Example A-208**

4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]pyridine

Step 1: Preparation of 4-fluorobenzoyl-4'-pyridyl methane

To a mixture of 4-picoline (32.6 g, 0.35 moles) and ethyl-4-fluorobenzoate (50.45g, 0.3 moles), maintained at 20 °C, was added lithium bis(trimethylsilylamide) (600 mL (1M)) in a steady but rapid stream so as to maintain ambient temperature. The initial yellow solution turned into a suspension which was then stirred for an additional 2 hours. Toluene (250 mL) was added and the mixture cooled to 0 °C. The reaction mixture was quenched with concentrated HCl at 0 °C to lower the pH to about 7. The organic layer was separated and the aqueous layer re-extracted with of toluene (100 mL). The organic layer was dried (sodium sulfate) and concentrated, to furnish a yellow solid which on trituration with hexanes (200 mL) provided the pure desoxybenzoin, 4-fluorobenzoyl-4'-pyridyl methane, in 90% yield (58g). <sup>1</sup>H NMR was consistent with the proposed structure.

Step 2:

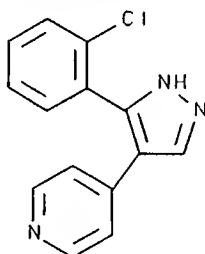
To a suspension of the desoxybenzoin prepared in step 1 (30g, 0.14 moles) in tetrahydrofuran (50 mL) was added dimethylformamide dimethyl acetal (50 mL) and the mixture stirred at ambient temperature for two days. The solution was then concentrated to dryness and the solid paste obtained was triturated with hexanes (150 mL) to furnish a yellow solid which was of sufficient purity (as determined by NMR) and was used for the next step without additional purification. Yield: 33.9 g (90%). <sup>1</sup>H NMR was consistent with the proposed structure.

Step 3:

The vinyl amine prepared in step 2 (33.9g, 0.1255 moles) was dissolved in 125 mL of ethanol and cooled to 0 °C. Hydrazine hydrate (8.0g of anhydrous or 16.0g. of hydrate, 0.25 moles) was then added in one portion. The mixture was stirred well and allowed to warm up to

278

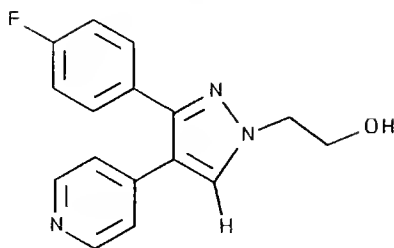
ambient temperature for a total reaction time of 3 hours. The mixture was concentrated and taken up in 200 mL of chloroform. After washing with water (100 mL), the organic layer was extracted with 150 mL of 10% HCl. The water layer was then treated with 0.5 g of activated charcoal at 70 °C for 10 minutes, filtered through celite and neutralized cautiously to pH 7 - 8 with vigorous stirring and cooling (20% sodium hydroxide was used). The fine off-white precipitate was filtered and dried to give 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]pyridine. Yield: 27.3g. (91%). Mass spectrum:  $m/z = 240$ .  $^1\text{H}$  NMR was consistent with the proposed structure. Anal. calc'd for  $\text{C}_{14}\text{H}_{10}\text{FN}_3$ : C, 70.28; H, 4.21; N, 17.56. Found: C, 70.11; H, 4.33; N, 17.61.

**Example A-209****4-[3-(2-chlorophenyl)-1H-pyrazol-4-yl]pyridine**

This compound was prepared by the same procedure described for Example A-208 using the corresponding starting reagents.

Anal. Calc'd for  $\text{C}_{14}\text{H}_{10}\text{ClN}_3$ : C, 65.76; H, 3.94; N, 16.43. Found: C, 65.22; H, 3.91; N, 16.50. m.p. (DSC): 208.46 °C.

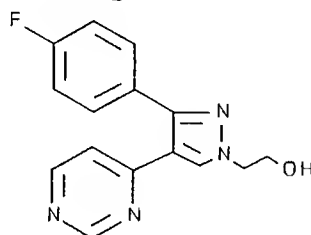
The compounds of Examples A-210 and A-211 illustrate were prepared in accordance with the chemistry described above (particularly in Scheme X):

**Example A-210****3-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazole-1-ethanol**

The desoxybenzoin prepared in step 1 of Example A-208, 4-fluorobenzoyl-4'-pyridyl methane, (12.7g, 0.059 moles) was mixed with 90% hydroxyethyl hydrazine (5.3g, 0.062 moles) in 30 mL of ethanol containing 0.5 mL of acetic acid in a 500 mL Erlenmeyer flask. After gentle boiling (1 hour), a small sample was evacuated at high vacuum and examined by <sup>1</sup>H NMR to confirm completion of hydrazone formation. On cooling to ambient temperature, the reaction mass solidified to a yellow cake. DMF dimethylacetal (36 mL, 0.27 moles) was then added and the mixture heated to 80°C for 10min, at which point all the solids dissolved and a clear yellow viscous solution was obtained. The reaction mixture was immediately allowed to cool slowly to 25 °C, and water (20 mL) was added dropwise with stirring, at which point a cloudy yellow oily suspension was obtained. The solution was now warmed to approximately 50-60 °C, whereupon the solution turned clear yellow. Slow cooling to ambient temperature with stirring (a crystal seed if available speeds up the process) results in a copious formation of crystals. Suction filtration followed by washing with 10% ethanol-water (50 mL), followed by drying, furnishes 3-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazole-1-ethanol as a light yellow crystalline solid. Re-heating the filtrate to clarity as before, followed by cooling, yields additional product. The third and fourth recovery from

280

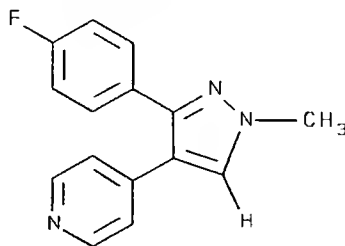
the mother liquor on standing overnight furnishes the remaining 3-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazole-1-ethanol. Total yield: {12.3 + 3.3 + 0.4 + 0.4} = 16.4g. (97.6%). Mass spectrum,  $m/z$  = 284.  $^1\text{H}$  NMR was consistent with the proposed structure. Anal. calc'd for  $\text{C}_{16}\text{H}_{14}\text{FN}_3\text{O}$  +  $\text{H}_2\text{O}$ : C, 63.78; H, 5.35; N, 13.95. Found: C, 63.55; H, 5.07; N, 13.69.

**Example A-211**

3-(4-fluorophenyl)-4-(4-pyrimidinyl)-1H-pyrazole-1-ethanol

This compound was prepared by the same procedure as described for Example A-210 except that the 4-picoline used to synthesize the desoxybenzoin was replaced with 4-methyl-pyrimidine.

The compound of Example A-212 was prepared in accordance with the chemistry of Scheme XI:

**Example A-212**

4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]pyridine

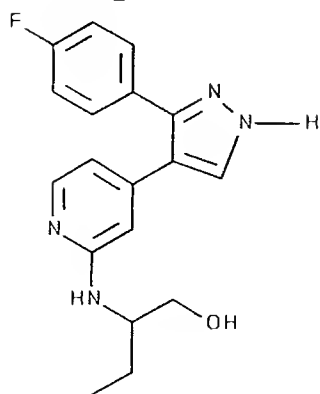
The vinyl amine prepared in Step 2 of Example A-208 (5.0g, 0.0185 moles) was taken up in ethanol (75mL) and

cooled to 0 °C. Methyl hydrazine (1.7g, 0.037 moles) in ethanol (75mL) was added in one portion while maintaining the temperature at 0 to 10 °C. After 3 hours at ambient temperature the solvent was removed and the residue taken up in methylene chloride (150 mL) and water (100 mL). The organic layer was separated, dried and concentrated to provide the crude regio-isomeric mixture as a light tan colored solid (80:20 by NMR in favor of the title compound). The crude isomeric mixture was taken up in 10% HCl (100 mL) and washed with methylene chloride (100 mL) and the water layer treated with activated charcoal (0.5g). After filtration through Celite, the solution was neutralized with sodium hydroxide (20%) to pH 8 with good stirring and cooling. The cream colored precipitate was filtered, washed with water and dried. The solid (5 g) was dissolved in hot 10% heptane/toluene (70 mL) and allowed to cool slowly, first to ambient temperature and then to 15 °C. Scratching the sides of the flask starts the crystallization process. After 2 hours of standing, the solids formed were filtered, washed with cold 50% toluene/heptane (25 mL) followed by hexane (25 mL) and dried to yield the pure title compound. <sup>1</sup>H NMR confirmed the structure (including regiochemistry using NOE experiments). Yield: 2.1g. (45%). Mass spectrum, m/z = 254 (base peak). Anal. calc'd for C<sub>15</sub>H<sub>12</sub>FN<sub>3</sub> + 0.2 H<sub>2</sub>O: C, 70.15; H, 4.86; N, 16.4. Found: C, 70.18; H, 4.6; N, 16.47.

The compound of Example A-213 was prepared in accordance with the chemistry of Scheme XII:



282

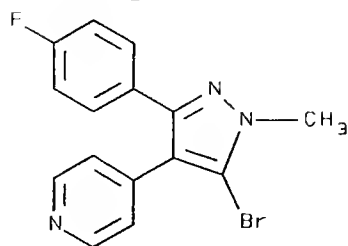
**Example A-213**

2-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]-1-butanol

An intimate mixture of 2-fluoro-pyridinyl pyrazole (0.2g, (prepared by the same procedure as described for Example A-210 except that the 4-picoline used to synthesize the desoxybenzoin was replaced with 2-fluoro-4-methylpyridine) and (R,S)-2-amino-1-butanol (4 fold molar excess) was heated to 210-220 °C in a sealed vial for 1.5 hours. After cooling to 100 °C the vial was cautiously opened and 5 mL of toluene and 5 mL of water were added and stirred well for 1 hour. The solid obtained, 2-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]-1-butanol, was suction-filtered and washed with an additional 5 mL of water followed by toluene and dried. Yield: 190mg. (71%). Mass spectrum,  $m/z = 343$ .  $^1\text{H}$  NMR was consistent with the proposed structure.

The compound of Example A-214 was prepared in accordance with the chemistry of Scheme XIII:

283

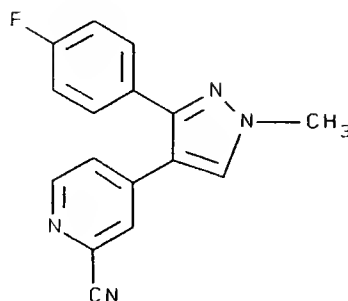
**Example A-214**

4-[5-bromo-3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]pyridine

To a solution of 4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]pyridine (2.7 g, 10.67 mmol) (prepared in accordance with Example A-212) in acetic acid (30 mL) and DMF (13 mL) was added bromine (19.5 g, 122.0 mmol). The solution was heated at 80 °C overnight. TLC indicated that the reaction was complete. The mixture was quenched slowly with  $K_2CO_3$  (25g). When pH was about 5, a precipitate was formed. The precipitate was washed with water (50mL x 5) to give 4-[5-bromo-3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]pyridine (1.24g, 35%): mp 174.38°C; Mass spectrum  $m/z$  = 332, 334;  $^1H$  NMR was consistent with the proposed structure. Anal. Calc'd for  $C_{15}H_{11}N_3FBr \cdot 0.2 H_2O$ : C, 53.66; H, 3.42; N, 12.51. Found: C, 53.58; H, 3.12; N, 12.43.

The compound of Example A-215 was prepared in accordance with the chemistry of Scheme XIV:

284

**Example A-215**

4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinecarbonitrile

Step 1:

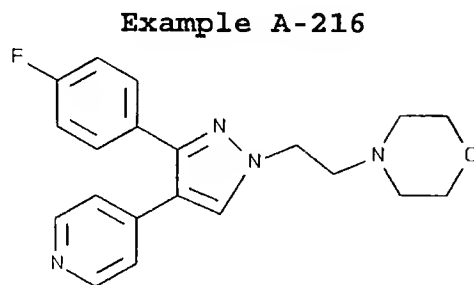
To a solution of 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]pyridine (4.3g, 17.97 mmol) (prepared in accordance with Example A-208) in methanol (100 mL) was added 3-chloroperoxybenzoic acid (5.44 g in 57 % purity, 17.97 mmol). The solution was stirred at 25 °C for overnight. The mixture was concentrated. K<sub>2</sub>CO<sub>3</sub> (10%, 100 mL) was added to the residue. A precipitate was formed, filtered and washed with water (30 mL x 3) to give the corresponding N-oxide (3.764g, 81.66%).

Step 2:

To a suspension of the N-oxide prepared in step 1 (0.40 g, 1.567 mmol) in DMF (5 mL) was added trimethylsilyl cyanide (0.3 mL, 2.25 mmol). The mixture was stirred for 15 minutes at 25 °C. Dimethylcarbamy l chloride (0.8 mL, 8.69 mmol) was added. The mixture was stirred at 25 °C for 2 hours. TLC indicated that the starting materials were gone. The mixture was partitioned into ethyl acetate:water (100 mL:20 mL). The organic layer was washed with K<sub>2</sub>CO<sub>3</sub> (10%, 20 mL), water (50 mL), brine (50 mL), dried over MgSO<sub>4</sub>, filtered and concentrated to give 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinecarbonitrile (0.23 g, 56 % yield): mp 209.22 °C ; Mass spectrum (chemical ionization): m/z =

265;  $^1\text{H}$  NMR was consistent with the proposed structure. Anal. Calc'd for  $\text{C}_{15}\text{H}_9\text{N}_4\text{F}\cdot 0.2 \text{ H}_2\text{O}$ : C, 67.26; H, 3.54; N, 20.92. Found: C, 67.44; H, 3.40; N, 20.69.

The compound of Example A-216 was prepared in accordance with the chemistry of Scheme XV:



4-[2-[3-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-1-yl]ethyl]morpholine

Step 1:

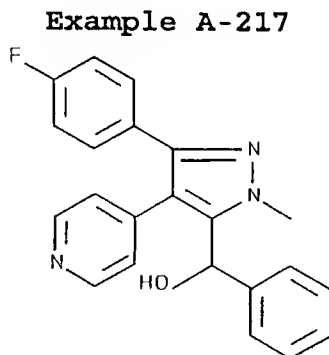
3-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazole-1-ethanol (prepared in accordance with Example A-210) (10.0 g, 0.0353 moles) was suspended in pyridine (100 mL) and cooled to 0 °C. Methane sulfonyl chloride (4.4 g, 0.0388 moles) was added slowly while maintaining the temperature at 0 °C. After stirring overnight at 10 °C, chilled water (100 mL) and methylene chloride (150 mL) was added and the two layers separated. The water layer was re-extracted with 100 mL of methylene chloride and the organic layer dried and concentrated to a paste. After drying at high vacuum, a light tan colored cake was obtained which was triturated with ether (75 mL), filtered and dried to furnish a cream colored solid in 79% yield (10.1g).  $^1\text{H}$  NMR was consistent with the proposed structure. The compound was used as such for step 2.

Step 2:

The mesylate prepared in step 1 (5.0 g, 0.0138

moles) was dissolved in an eight fold excess of morpholine (9.6 g, 0.11 moles) in methanol (50 mL) and heated at reflux for 3 to 4 hours. After an NMR sample confirmed completion, the mixture was concentrated and taken up in methylene chloride (150 mL) and washed with water (100 mL) and then with 75 mL of 5% HCl. The water layer was neutralized to pH 8 and extracted with methylene chloride (100 mL). On drying and concentration a light yellow pasty solid was obtained which was triturated with 25 mL of ether to furnish a solid. Recrystallization from toluene/hexane provided 4-[2-[3-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-1-yl]ethyl]morpholine as a solid. Yield: 4.5g (86%). Mass spectrum,  $m/z = 353$ .  $^1\text{H}$  NMR was consistent with the proposed structure. Anal. calc'd for  $\text{C}_{20}\text{H}_{21}\text{FN}_4\text{O}$ : C, 68.16; H, 6.01; N, 15.90. Found: C, 68.20; H, 6.21; N, 15.80.

The compound of Example A-217 was prepared in accordance with the chemistry of Scheme XVI:



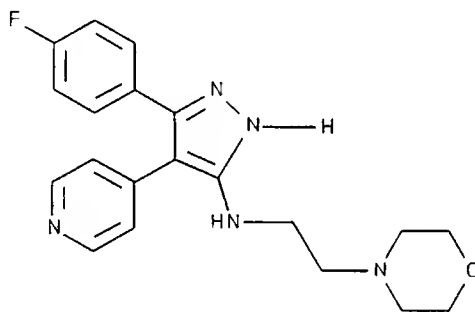
3-(4-fluorophenyl)-1-methyl- $\alpha$ -phenyl-4-(4-pyridinyl)-1H-pyrazole-5-methanol

To solid magnesium (60 mg, 5 mmol) under nitrogen was added a solution of 4-[5-bromo-3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]pyridine (450 mg, 1.35 mmol) (prepared in accordance with Example A-214) in tetrahydrofuran (7 mL). The mixture was heated at 40 °C

for 2 hours. Benzaldehyde (1 mL) was added. The mixture was heated to 45 °C for 2 hours. It was quenched with HCl (10 mL, 1N) and washed with ethyl acetate. The aqueous acid layer was basified and extracted with ethyl acetate. The organic layer was washed with water, brine, dried over  $\text{MgSO}_4$ , filtered and concentrated to give a residue. The residue was purified with a silica gel column to give the title compound (59 mg, 12% yield). MS:  $m/z = 360$  ( $M+1$ );  $^1\text{H}$  NMR was consistent with the proposed structure. Anal. Calc'd for  $\text{C}_{22}\text{H}_{18}\text{N}_2\text{OF} \cdot 0.6\text{EtOAc}$ : C, 71.1; H, 5.6; N, 10.2; Found: C, 70.9; H, 5.47; N, 10.2.

The compound of Example A-218 was prepared in accordance with the chemistry described above (particularly Scheme XVII):

**Example A-218**

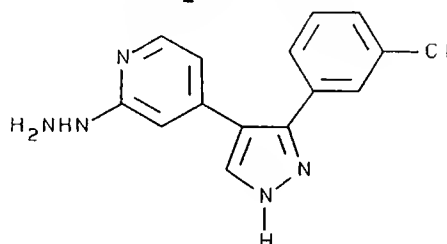


N-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-morpholineethanamine

The starting desoxybenzoin prepared in step 1 of Example A-208, 4-fluorobenzoyl-4'-pyridyl methane, (1.0 g, 0.0046 moles) was dissolved in 10 mL of DMF and cooled to -10 °C (dry ice-aqueous isopropanol). N-chlorosuccinimide (0.62 g, 0.0046 moles) was added in one portion while maintaining the temperature at -10 °C. After 5 minutes the thiosemicarbazide (0.0046 moles) was added in one portion at 0 °C and allowed to warm to ambient temperature slowly over 1 hour. After stirring overnight, the solvent was removed at high vacuum and

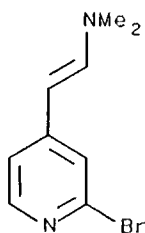
288

water and toluene (25 mL each) added and stirred well. The toluene layer was separated and the water layer (starting pH of 5.5) treated with bicarbonate to pH 8. The fine precipitate formed was filtered and washed with water, toluene and ether. A final trituration with ether (25 mL) furnished an off white solid, N-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-morpholineethanamine, which was re-filtered and dried. Yield: 0.95g. (56%). Mass Spec. m/z: 368 (base peak). Anal. Calc'd for  $C_{20}H_{22}FN_5O$ . C, 65.38; H, 6.04; N, 19.06. Found: C, 64.90; H, 5.92; N, 18.67.

**Example A-219**

4-[3-(3-chlorophenyl)-1H-pyrazol-4-yl]-2(1H)-pyridinone hydrazone

Step 1: Preparation of (E)-2-(2-bromo-4-pyridinyl)-N,N-dimethylethanamine

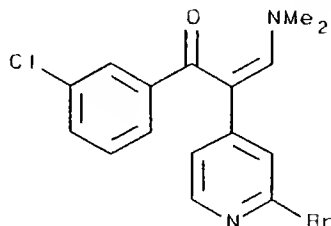


4-Methyl-2-bromopyridine (1.0 g, 5.8 mmol) and t-butoxybis(dimethylamino)methane (5 ml) were heated to 150 °C for 16 hours. 4-Methyl-2-bromopyridine was prepared as set forth in B. Adger et al., J. Chem. Soc., Perkin Trans. 1, pp. 2791-2796 (1988), which is incorporated herein by reference. The contents were evaporated and the residue dissolved in ethyl acetate and washed with

289

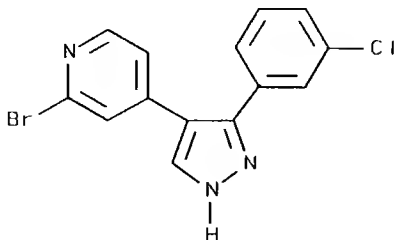
water. The organic layer was dried over magnesium sulfate and solvent removed in vacuo to give 1.0 g of (E)-2-(2-bromo-4-pyridinyl)-N,N-dimethylethenamine as an oil suitable for use in step 2.

Step 2: Preparation of (Z)-2-(2-bromo-4-pyridinyl)-1-(3-chlorophenyl)-3-(dimethylamino)-2-propen-1-one



The product from step 1 (1.0 g, 4.4 mmol) was dissolved in methylene chloride (15 ml). Triethylamine (900 mg, 8.8 mmol) was added at 0 °C, followed by the addition of 3-chlorobenzoyl chloride (350 mg, 4.5 mmol). The mixture was stirred under nitrogen for 16 hours. Solvent was evaporated in vacuo and the residue was dissolved in ether (25 ml), stirred with magnesium sulfate (500 mg) and silica gel (500mg), and filtered. Ether was evaporated and the residue was chromatographed on silica gel using mixtures of acetone and methylene chloride as eluents to give 670 mg of the product, (Z)-2-(2-bromo-4-pyridinyl)-1-(3-chlorophenyl)-3-(dimethylamino)-2-propen-1-one, as a glass which was used in step 3 without further purification.

Step 3: Preparation of 2-bromo-4-[3-(3-chlorophenyl)-1H-pyrazol-4-yl]pyridine

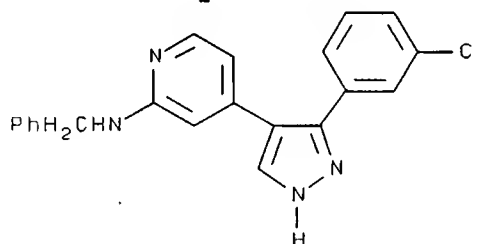




A solution of the product from step 2 (650 mg, 1.8 mmol) and hydrazine monohydrate (100 mg) in ethanol (10 ml) was refluxed for 24 hours. Solvent was evaporated and the residue was chromatographed on silica gel using mixtures of ethyl acetate and toluene as eluents to give 2-bromo-4-[3-(3-chlorophenyl)-1H-pyrazol-4-yl]pyridine (190 mg, 31%) as an oil: Anal. Calc'd for  $C_{14}H_9BrClN_3$ : C, 50.25; H, 2.71; N, 12.56. Found: C, 50.10; H, 2.60; N, 12.40.

Continued elution with mixtures of ethyl acetate and methanol gave 4-[3-(3-chlorophenyl)-1H-pyrazol-4-yl]-2(1H)-pyridinone hydrazone (190 mg, 36%) as a crystalline solid: m.p. 163-164 °C.; MS (M+H) = 286. Anal. Calc'd for  $C_{14}H_{12}N_5Cl$ : C, 58.85; H, 4.23; N, 24.51. Found: C, 58.53; H, 4.28; N, 24.87.

**Example A-220**



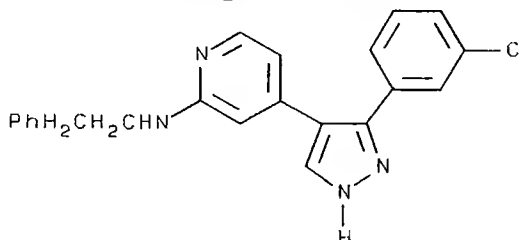
4-[3-(3-chlorophenyl)-1H-pyrazol-4-yl]-N-(phenylmethyl)-2-pyridinamine

A solution of the bromopyridine compound prepared in step 3 of Example A-219 (150 mg, 0.5 mmol) in benzylamine (5 ml) was heated at 175 °C for six hours. After cooling, excess benzylamine was removed by high vacuum distillation and ethyl acetate added to the residue. After washing the organic phase with water and drying over magnesium sulfate, the solvent was removed in vacuo and the residue chromatographed on silica gel using mixtures of ethyl acetate and toluene to give 4-[3-(3-

291

chlorophenyl)-1H-pyrazol-4-yl]-N-(phenylmethyl)-2-pyridinamine (110 mg, 61%) as a solid, m.p. 179-180 °C.

Anal. Calc'd For  $C_{21}H_{17}ClN_4$ : C, 69.90; H, 4.75; N, 15.53.  
Found: C, 69.69; H, 4.81; N, 15.11.

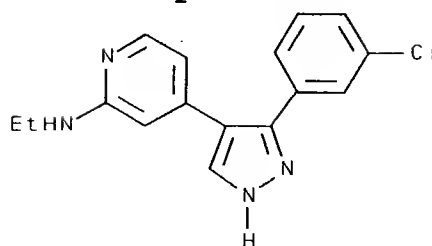
**Example A-221**

4-[3-(3-chlorophenyl)-1H-pyrazol-4-yl]-N-(phenylethyl)-2-pyridinamine

A solution of the bromopyridine compound prepared in step 3 of Example A-219 (250 mg, 0.75 mmol) in phenethylamine (5 ml) was heated at 175 °C for six hours under a nitrogen atmosphere. The excess amine was distilled off under high vacuum and the residue was dissolved in ethyl acetate and washed with water. After drying over magnesium sulfate and removal of solvent, the residue was chromatographed on silica gel with mixtures of ethyl acetate and toluene to give 4-[3-(3-chlorophenyl)-1H-pyrazol-4-yl]-N-(phenylethyl)-2-pyridinamine (230 mg, 81%) as a solid, m.p. 185-186 °C.

Anal. Calc'd For  $C_{22}H_{19}ClN_4$ : C, 70.49; H, 5.11; N, 14.95. Found: C, 70.29; H, 5.15; N, 14.66.

292

**Example A-222**

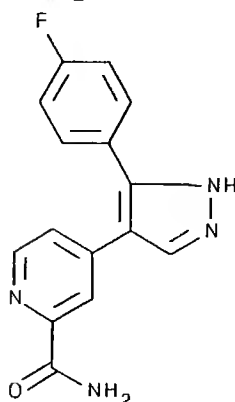
4-[3-(3-chlorophenyl)-1H-pyrazol-4-yl]-N-ethyl-2-pyridinamine

A solution of the bromopyridine compound prepared in step 3 of Example A-219 (300 mg, 0.9 mmol) in ethylamine (3.5 ml) and ethanol (5 ml) as heated at 150 °C in a sealed tube for 9 hours. The solvent was removed in vacuo and the residue chromatographed on silica gel with 70 ethyl acetate/30 toluene to give 4-[3-(3-chlorophenyl)-1H-pyrazol-4-yl]-N-ethyl-2-pyridinamine (125 mg, 46%) as a solid, m.p. 186-187 °C.

Anal. Calc'd For  $C_{16}H_{15}ClN_4$ : C, 64.32; H, 7.06; N, 18.75.  
Found: C, 64.42; H, 7.01; N, 18.45.

The compounds of Examples A-223 through A-226 were synthesized in accordance with the chemistry described above (particularly in Scheme XVIII) by selection of the corresponding starting reagents:

293

**Example A-223**

4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinecarboxamide

Step 1:

To a suspension of 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]pyridine (prepared as set forth in Example A-208) (8.8 g, 0.037 mol) in methylene chloride was added m-chloroperoxybenzoic acid (mCPBA) in one portion at room temperature. After stirring for 16 hours, solvent was removed and the residue was treated with saturated sodium bicarbonate solution. The precipitate was filtered, air-dried to give 8.2 g of a product as a white solid (87%), mp: 207-209°C.

Step 2: Preparation of 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinecarbonitrile

To a solution of the product of step 1 (5.1 g, 0.02 mol) in 20 mL of DMF was added trimethylsilyl cyanide (2.5 g, 0.025 mol), followed by a solution of N, N-dimethylcarbamoyl chloride (2.7 g, 0.025 mol) in 5 mL of DMF at room temperature. After stirring overnight, the reaction mixture was basified by 200 mL of 10% potassium carbonate water solution. The aqueous phase was extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated and the crude

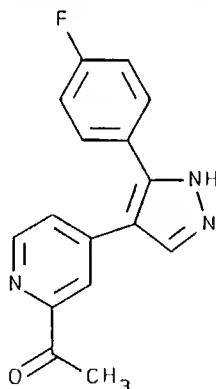
294

was triturated with hexane and filtered to give 4.3 g of 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinecarbonitrile (90%) as a pale yellow solid, mp: 238-239°C.

Step 3: Preparation of 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinecarboxamide:

To a solution of 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinecarbonitrile from step 2 (0.45 g, 0.0017 mol) in 10 mL of DMSO was added hydrogen peroxide (0.24 mL of 30% aqueous solution, 1.7 mmol) and potassium carbonate (0.04 g, 0.4 mmol) at 0°C. The mixture was stirred for 1 hour while allowing it to warm to room temperature. Water was added and the precipitate was collected by filtration and air-dried to give 0.32 g of 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinecarboxamide as a white solid (67% yield), mp: 230-231 °C. Anal. Calc'd for C<sub>15</sub>H<sub>11</sub>FN<sub>4</sub>O: C, 63.83; H, 3.93; N, 19.85. Found C, 63.42; H, 3.66; N, 19.58.

**Example A-224**

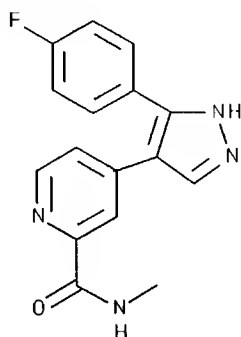


**Methyl 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinecarboxylate**

To a suspension of 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinecarboxamide prepared as set forth in Example A-223 (2.9 g, 0.01 mol) in 50 mL of methanol was added N,N-dimethylformamide dimethyl acetal (3.67 g, 0.03

295

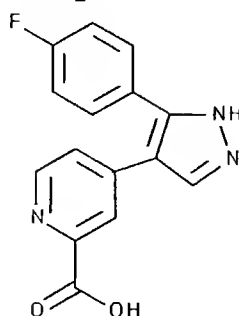
mol) dropwise. The reaction mixture was stirred at room temperature overnight and heated at reflux for 4 hours. After cooling, the precipitate was collected by filtration and air-dried to give 2.0 g of methyl 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinecarboxylate as a white solid (69% yield), mp: 239-241°C. Anal. Calc'd for  $C_{16}H_{12}FN_3O_2$ : C, 64.64; H, 4.07; N, 14.13. Found: C, 64.36; H, 4.10; N, 14.27.

**Example A-225**

4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N-methyl-2-pyridinecarboxamide

A mixture of methyl 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinecarboxylate prepared as set forth in Example A-224 (0.45 g, 1.5 mmol) and 20 mL of methylamine (40% aqueous solution) was heated at 120°C in a sealed tube for 16 hours. After cooling, water was added and the aqueous phase was extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated to afford 0.4 g of 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N-methyl-2-pyridinecarboxamide as a white solid, mp: 88-89°C. Anal. Calc'd for  $C_{16}H_{13}FN_4O + 0.4 H_2O$ : C, 63.32; H, 4.58; N, 18.46. Found C, 63.10; H, 4.62; N, 18.35.

296

**Example A-226**

4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinecarboxylic acid

To a solution of 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinecarboxylate prepared as set forth in Example A-224 (0.90 g, 0.003 mol) in 10 mL of ethanol was added a solution of sodium hydroxide (0.24 g, 0.006 mol) in 5 mL of water. The reaction mixture was heated at reflux for 10 hours. After the removal of solvent, the residue was dissolved in water and acidified with citric acid solution to pH 5. Then the aqueous phase was extracted with ethyl acetate and the organic phase was dried over magnesium sulfate and concentrated. The crude was purified by treating with ether to give 0.62 g of 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinecarboxylic acid as a white solid (73% yield), mp: 245°C(dec). Anal Calc'd for  $C_{15}H_{10}FN_3O + 0.2 H_2O$ : C, 62.80; H, 3.65; N, 14.65. Found: C, 62.77; H, 3.42; N, 14.58.

Additional compounds of the present invention which were prepared according to one or more of above reaction schemes (particularly Schemes IX through XVIII) are disclosed in Table 3. The specific synthesis scheme or schemes as well as the mass spectroscopy and elemental analysis results for each compound also are disclosed in Table 3.

TABLE 3

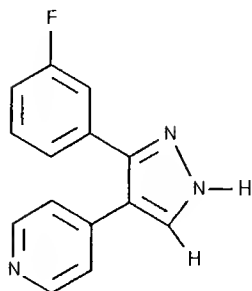
Example	General Procedure	MS M+1	Microanalysis							
			C calc	C found	H calc	H found	N calc	N found	water added	EtOAc added
A-227	IX	240	69	69	4.3	4.6	17.2	16.8	0.25	
A-228	IX	266	65.69	65.69	4.41	4.33	15.32	14.98		
A-229	XI	254	70.6	70.6	4.8	4.5	16.5	16.3	0.1	
A-230	IX	256	65.76	65.48	3.94	3.78	16.43	16.52		
A-231	XI	280	64.18	63.95	4.39	4.31	13.86	13.90		
A-232	XI	271	66.79	66.79	4.48	4.24	15.58	15.32		
A-233	XI	284	66.9	66.8	5	5	14.6	14.9	0.2	
A-234	XI	270	65.9	65.6	4.6	4.6	15.4	15.4	0.2	
A-235	XI	264	77	76.7	6.5	6.5	15.8	15.7	0.1	
A-236	IX	221	75.38	75.44	5.06	5.1	18.84	19	0.1	
A-237	IX	290	61.52	61.67	3.58	3.51	14.35	14.32		
A-238	XI	304	63.36	63.28	3.99	3.91	13.85	13.83		
A-239	IX	258	65.37	65.39	3.53	3.52	16.33	16.31		
A-240	IX	274	61.44	61.14	3.31	3.01	15.35	14.95		
A-241	IX	300	56.02	55.99	3.36	3.26	14.00	14.01		
A-242	XI	272	66.42	66.41	4.09	4.04	15.49	15.32		
A-243	XI	314	57.34	57.22	3.85	3.68	13.37	13.27		
A-244	IX	342	76.39	76.16	4.81	4.51	12.31	12.05	0.25	
A-245	XII	341	64.89	64.65	6.36	6.17	15.93	15.82	0.6	
A-246	XII	391	66.08	66.18	5.04	5.56	14.01	12.26	0.5	
A-247	XII	362	64.46	64.16	4.65	4.34	18.79	18.65	0.6	
A-249	XII	258	64.91	64.84	3.58	3.63	16.22	15.98	0.1	



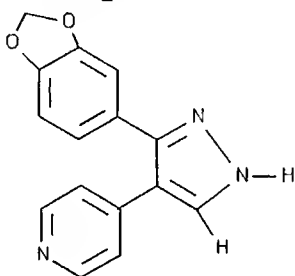
A-250	IX	348	48.44	48.07	2.9	2.82	12.1	12.01		
A-251	XI	362	49.88	49.89	3.35	3.51	11.63	11.54		
A-252	XI	304	63.36	63.34	3.99	3.96	13.85	13.81		
A-253	XII	377	68.24	68.17	5	4.71	14.47	14.34	0.6	
A-254	XII	363	66.31	66.12	4.77	4.31	14.73	14.6	1	
A-215	XIV	265	67.3	67.4	3.5	3.4	20.9	20.7	0.2	
A-255	XII	298	64.63	64.64	5.42	5.41	23.55	23.32		
A-256	XI	272	66.42	66.58	4.09	4.26	15.49	14.78		
A-257	IX	276	60.11	60.4	3.06	3.18	15.02	14.73	0.25	
A-258	IX	254								
A-259	XI	268	71.89	71.63	5.28	5.24	15.72	15.84		
A-260	X	290	62.28	62.41	3.48	3.48	14.53	14.51		
A-261	X, XV	311	69.26	69.2	6.2	6.25	17.95	17.89	0.1	
A-262	XI	376	72.71	72.5	5.17	4.98	11.06	10.99	0.25	
A-263	XII	428	70.81	70.59	6.28	6.45	15.88	15.08	0.75	
A-264	XII	326	63.79	63.76	6.39	6.09	20.66	20.45	0.75	
A-265	IX	400	66.18	66.77	4.1	4.23	16.78	15.83	1	
A-266	XII	368	62.32	62.38	6.28	6.5	18.17	17.56	1	
A-267	XI	302	62.66	62.85	4.47	4.34	13.7	13.53	0.4	
A-268	XII	349	62.9	63.2	5.2	4.8	22.7	22.5	0.75	0.1
A-269	XI, XV	371	61.85	61.84	5.71	5.24	14.42	14.17	1	
A-270	XI, XV	404	70.66	70.7	4.82	4.61	10.3	10.15	0.25	
A-271	XI, XV	329	65.8	65.3	5.5	5.6	17.1	16.8		
A-272	XI	406	69.95	70.13	5.35	5.28	10.14	9.89	0.5	
A-273	XI	354	66.9	67.2	6.9	6.6	19.1	18.7	0.2	0.1
A-274	XI, XII, XV	434	63.6	63.1	6.3	5.8	14.4	14	2	0.2



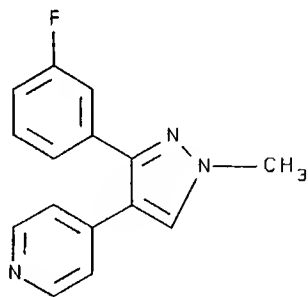
300

**Example A-227**

4-[3-(3-fluorophenyl)-1H-pyrazol-4-yl]pyridine

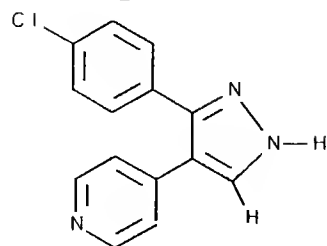
**Example A-228**

4-[3-(1,3-benzodioxol-5-yl)-1H-pyrazol-4-yl]pyridine

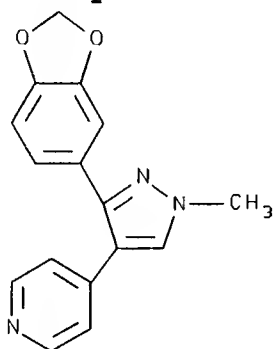
**Example A-229**

4-[3-(3-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]pyridine

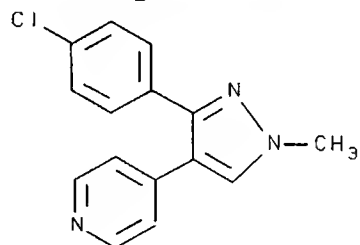
301

**Example A-230**

4-[3-(4-chlorophenyl)-1H-pyrazol-4-yl]pyridine

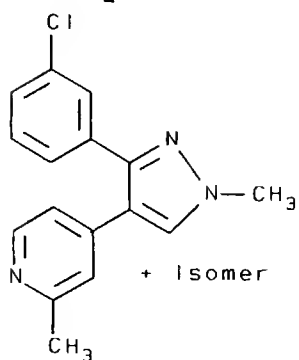
**Example A-231**

4-[3-(1,3-benzodioxol-5-yl)-1-methyl-1H-pyrazol-4-yl]pyridine

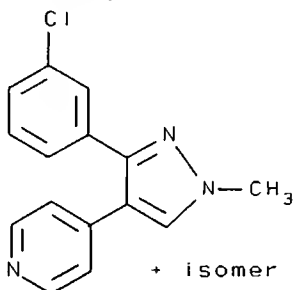
**Example A-232**

4-[3-(4-chlorophenyl)-1-methyl-1H-pyrazol-4-yl]pyridine

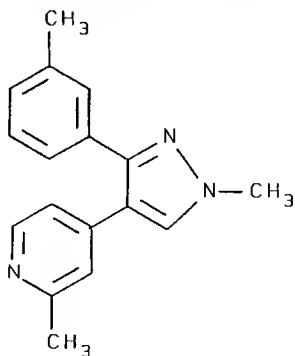
302

**Example A-233**

4-[3-(3-chlorophenyl)-1-methyl-1H-pyrazol-4-yl]-2-methylpyridine and 4-[5-(3-chlorophenyl)-1-methyl-1H-pyrazol-4-yl]-2-methylpyridine

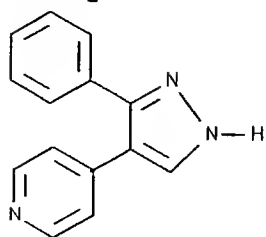
**Example A-234**

4-[3-(3-chlorophenyl)-1-methyl-1H-pyrazol-4-yl]pyridine and 4-[5-(3-chlorophenyl)-1-methyl-1H-pyrazol-4-yl]pyridine

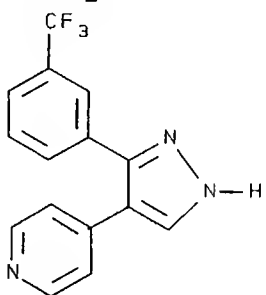
**Example A-235**

2-methyl-4-[1-methyl-3-(3-methylphenyl)-1H-pyrazol-4-yl]pyridine

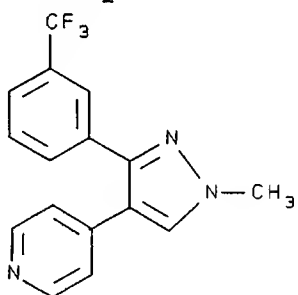
303

**Example A-236**

4-(3-phenyl-1H-pyrazol-4-yl)pyridine

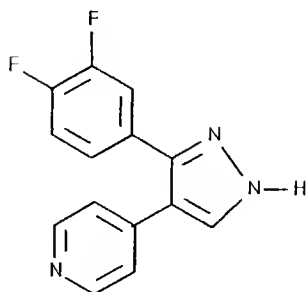
**Example A-237**

4-[3-[3-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl]pyridine

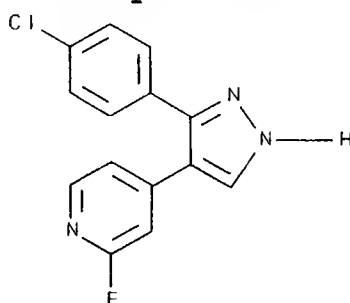
**Example A-238**

4-[1-methyl-3-[3-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl]pyridine

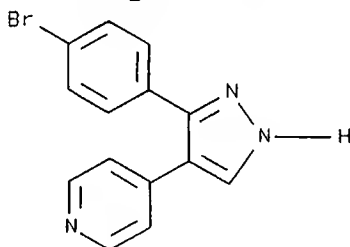
304

**Example A-239**

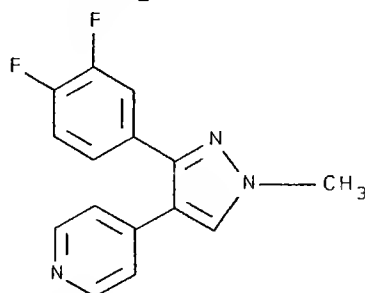
4-[3-(3,4-difluorophenyl)-1H-pyrazol-4-yl]pyridine

**Example A-240**

4-[3-(4-chlorophenyl)-1H-pyrazol-4-yl]-2-fluoropyridine

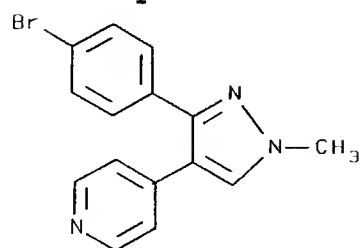
**Example A-241**

4-[3-(4-bromophenyl)-1H-pyrazol-4-yl]pyridine

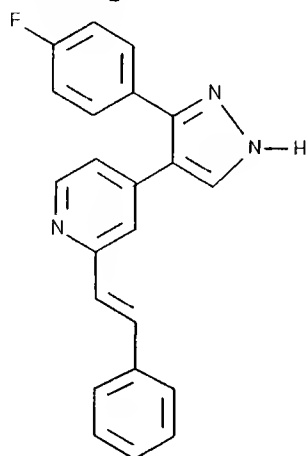
**Example A-242**

4-[3-(3,4-difluorophenyl)-1-methyl-1H-pyrazol-4-yl]pyridine

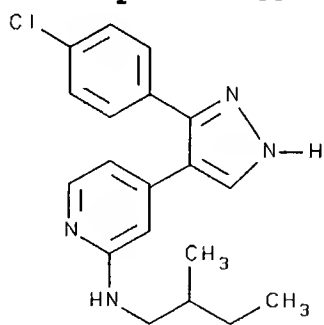
305

**Example A-243**

4-[3-(4-bromophenyl)-1-methyl-1H-pyrazol-4-yl]pyridine

**Example A-244**

(E)-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-(2-phenylethenyl)pyridine

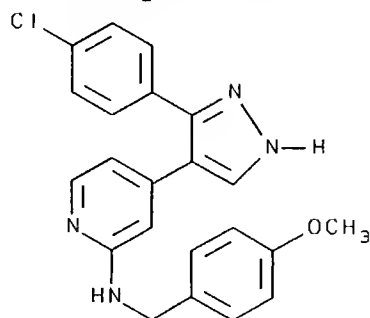
**Example A-245**

S

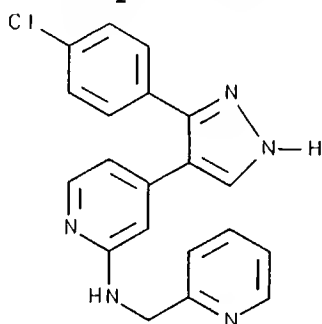


306

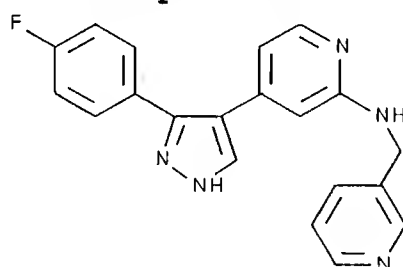
(S)-4-[3-(4-chlorophenyl)-1H-pyrazol-4-yl]-N-(2-methylbutyl)-2-pyridinamine

**Example A-246**

4-[3-(4-chlorophenyl)-1H-pyrazol-4-yl]-N-[(4-methoxyphenyl)methyl]-2-pyridinamine

**Example A-247**

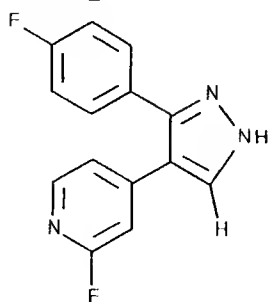
N-[4-[3-(4-chlorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]-2-pyridinemethanamine

**Example A-248**

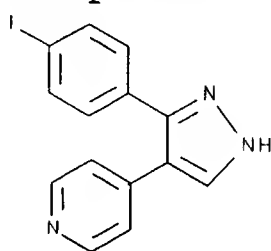
N-[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]-2-pyridinemethanamine

Anal Calc'd: C, 41.12; H, 3.58; N, 9.22. Found: C, 41.74; H, 5.05; N, 11.11.

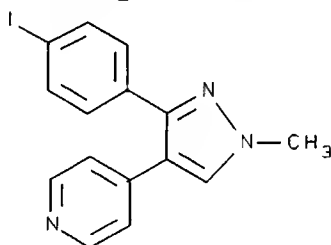
307

**Example A-249**

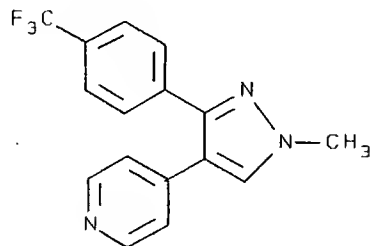
2-fluoro-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]pyridine

**Example A-250**

4-[3-(4-iodophenyl)-1H-pyrazol-4-yl]pyridine

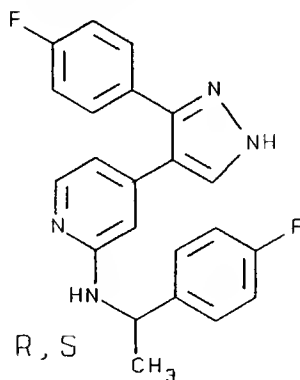
**Example A-251**

4-[3-(4-iodophenyl)-1-methyl-1H-pyrazol-4-yl]pyridine

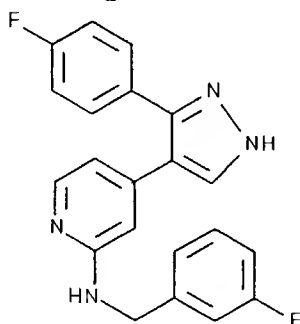
**Example A-252**

308

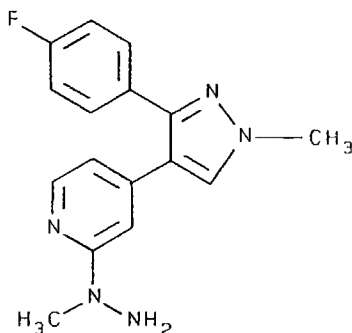
4-[1-methyl-3-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl]  
pyridine

**Example A-253**

N-[1-(4-fluorophenyl)ethyl]-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinamine

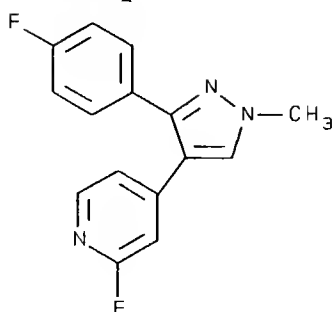
**Example A-254**

N-[(3-fluorophenyl)methyl]-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinamine

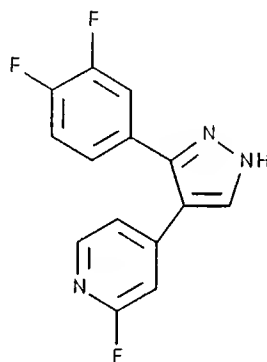
**Example A-255**

4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-2-(1-methylhydrazino)pyridine

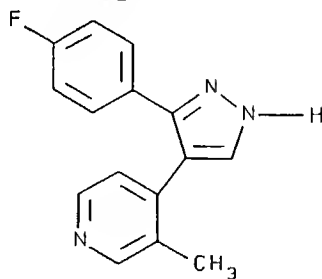
309

**Example A-256**

2-fluoro-4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]pyridine

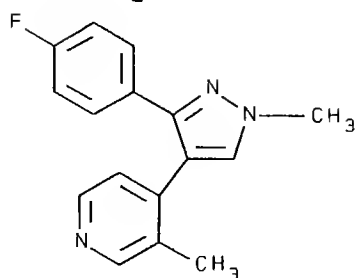
**Example A-257**

4-[3-(3,4-difluorophenyl)-1H-pyrazol-4-yl]-2-fluoropyridine

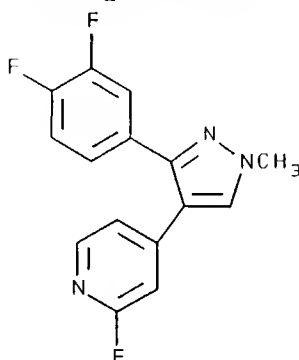
**Example A-258**

4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-3-methylpyridine

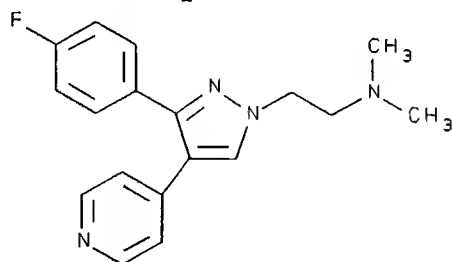
310

**Example A-259**

4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-3-methylpyridine

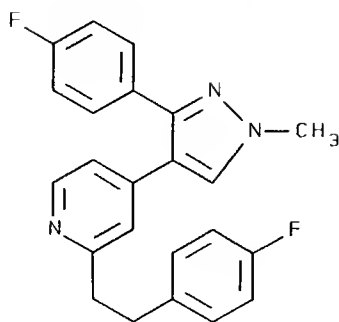
**Example A-260**

4-[3-(3,4-difluorophenyl)-1-methyl-1H-pyrazol-4-yl]-2-fluoropyridine

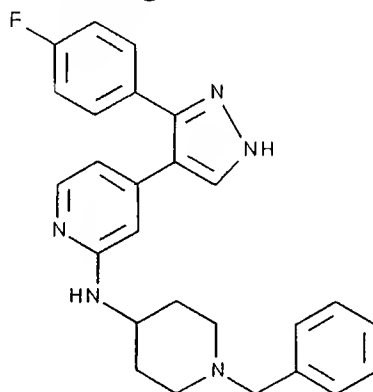
**Example A-261**

3-(4-fluorophenyl)-N,N-dimethyl-4-(4-pyridinyl)-1H-pyrazole-1-ethanamine

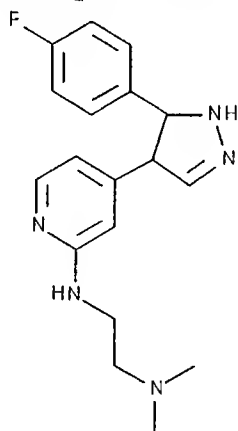
311

**Example A-262**

2-[2-(4-fluorophenyl)ethyl]-4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]pyridine

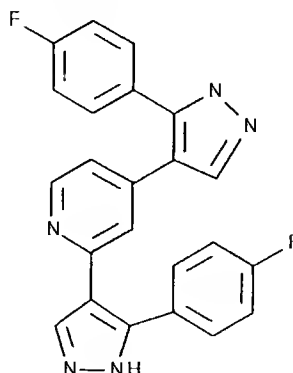
**Example A-263**

4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N-[1-(phenylmethyl)-4-piperidiny]l-2-pyridinamine

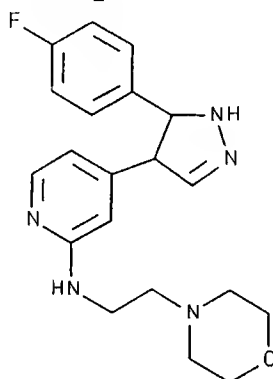
**Example A-264**

312

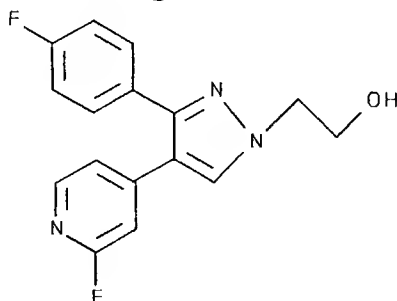
N' - [4 - [3 - (4-fluorophenyl) - 1H-pyrazol-4-yl] - 2-pyridinyl] -  
N,N-dimethyl-1,2-ethanediamine

**Example A-265**

2,4-bis[3-(4-fluorophenyl)-1H-pyrazol-4-yl]pyridine

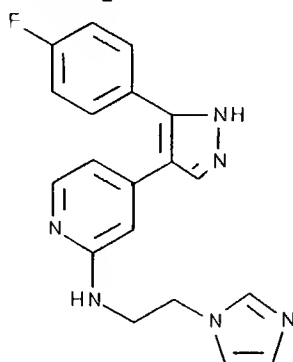
**Example A-266**

N - [4 - [3 - (4-fluorophenyl) - 1H-pyrazol-4-yl] - 2-pyridinyl] - 4 -  
morpholineethanamine

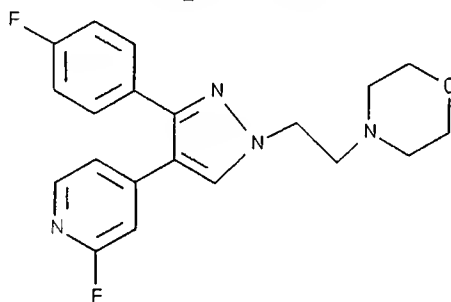
**Example A-267**

313

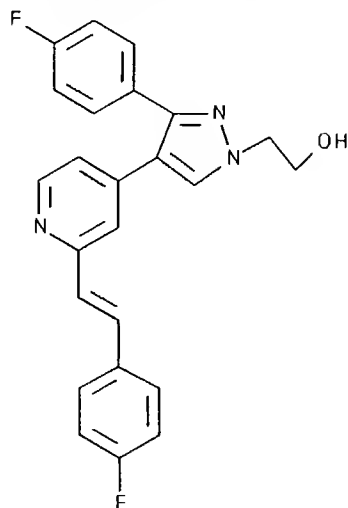
3-(4-fluorophenyl)-4-(2-fluoro-4-pyridinyl)-1H-pyrazole-1-ethanol

**Example A-268**

4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N-[2-(1H-imidazol-1-yl)ethyl]-2-pyridinamine

**Example A-269**

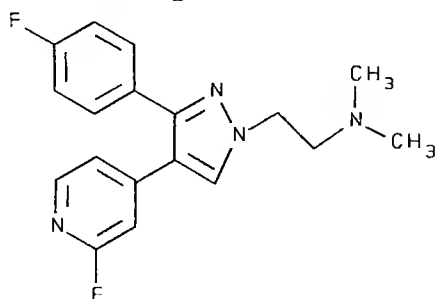
4-[2-[3-(4-fluorophenyl)-4-(2-fluoro-4-pyridinyl)-1H-pyrazol-1-yl]ethyl]morpholine

**Example A-270**

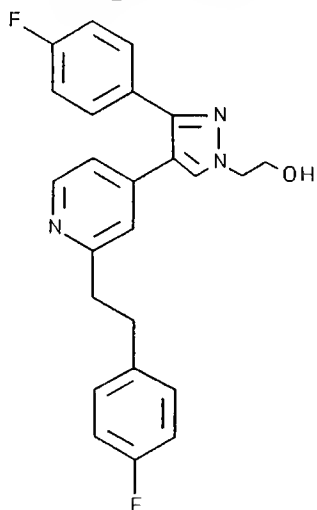


314

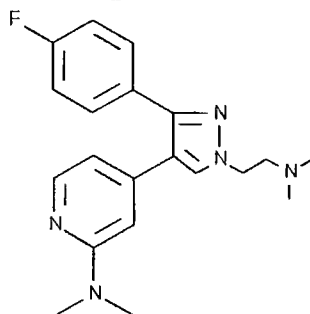
(E)-3-(4-fluorophenyl)-4-[2-[2-(4-fluorophenyl)ethenyl]-4-pyridinyl]-1H-pyrazole-1-ethanol

**Example A-271**

3-(4-fluorophenyl)-4-(2-fluoro-4-pyridinyl)-N,N-dimethyl-1H-pyrazole-1-ethanamine

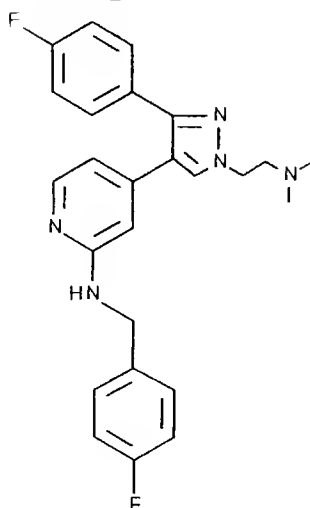
**Example A-272**

3-(4-fluorophenyl)-4-[2-[2-(4-fluorophenyl)ethyl]-4-pyridinyl]-1H-pyrazole-1-ethanol

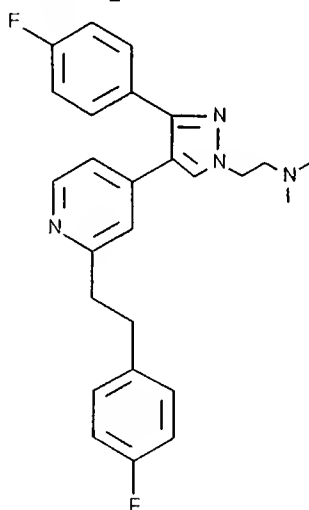
**Example A-273**

4-[1-[2-(dimethylamino)ethyl]-3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N,N-dimethyl-2-pyridinamine

315

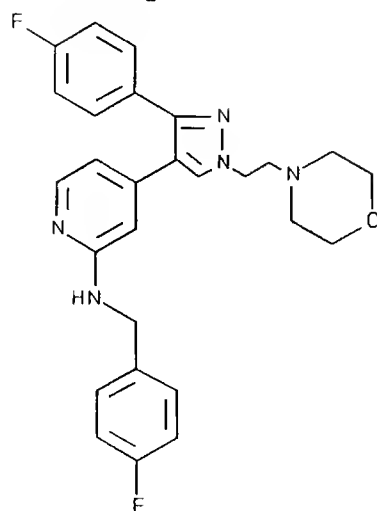
**Example A-274**

4-[1-[2-(dimethylamino)ethyl]-3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N-[(4-fluorophenyl)methyl]-2-pyridinamine

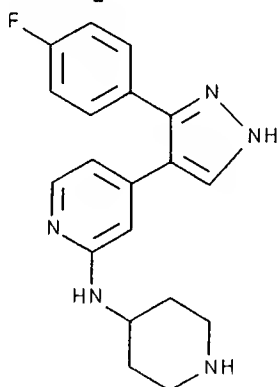
**Example A-275**

3-(4-fluorophenyl)-4-[2-[2-(4-fluorophenyl)ethyl]-4-pyridinyl]-N,N-dimethyl-1H-pyrazole-1-ethanamine

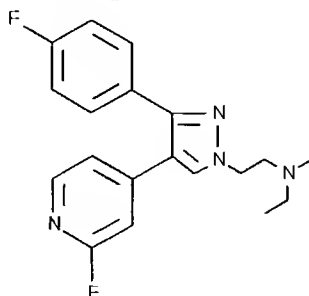
316

**Example A-276**

N-[(4-fluorophenyl)methyl]-4-[3(or 5)-(4-fluorophenyl)-1-[[2-(4-morpholinyl)ethyl]-1H-pyrazol-4-yl]-2-pyridinamine

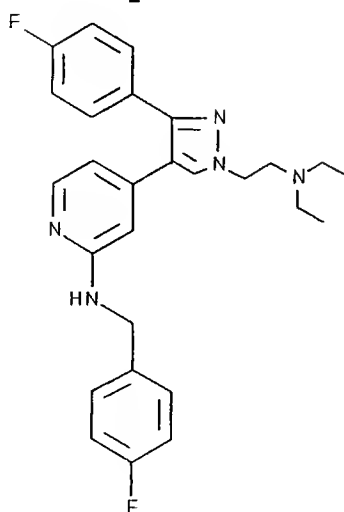
**Example A-277**

4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N-4-piperidinyl-2-pyridinamine

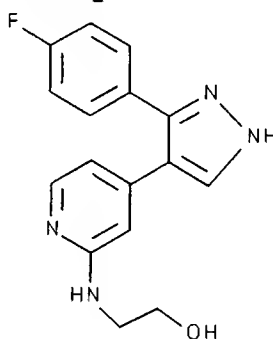
**Example A-278**

N,N-diethyl-3-(4-fluorophenyl)-4-(2-fluoro-4-pyridinyl)-1H-pyrazole-1-ethanamine

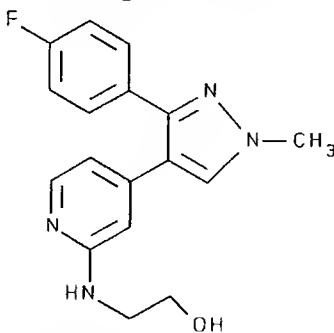
317

**Example A-279**

4-[1-[2-(diethylamino)ethyl]-3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N-[(4-fluorophenyl)methyl]-2-pyridinamine

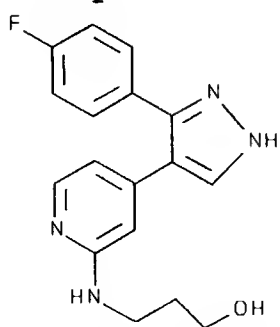
**Example A-280**

2-[[4-[3-(4-(fluorophenyl))-1H-pyrazol-4-yl]-2-pyridinyl]amino]ethanol

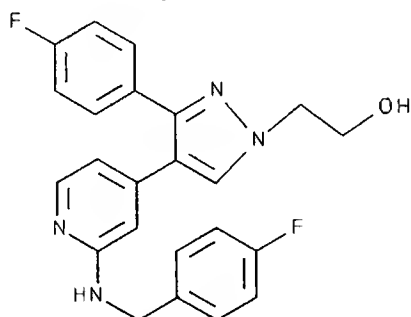
**Example A-281**

2-[[4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-2-pyridinyl]amino]ethanol

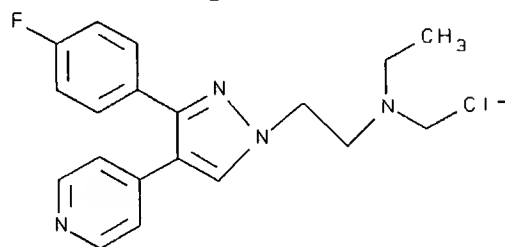
318

**Example A-282**

3-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]-1-propanol

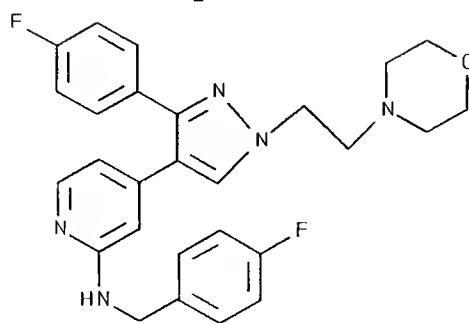
**Example A-283**

3 (or 5) - (4-fluorophenyl) -4- [2- [[4-fluorophenyl)methyl]amino] -4-pyridinyl] -1H-pyrazole-1-ethanol

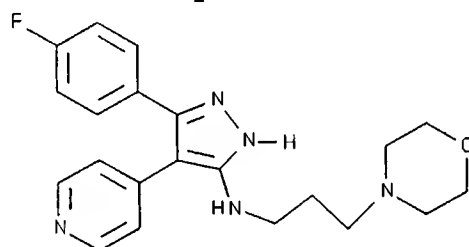
**Example A-284**

N,N-diethyl-3-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazole-1-ethanamine

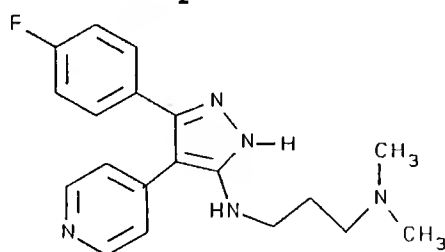
319

**Example A-285**

N-[(4-fluorophenyl)methyl]-4-[3-(4-fluorophenyl)-1-[2-(4-morpholinyl)ethyl]-1H-pyrazol-4-yl]-2-pyridinamine

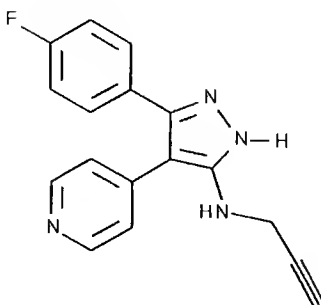
**Example A-286**

N-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-morpholinepropanamine

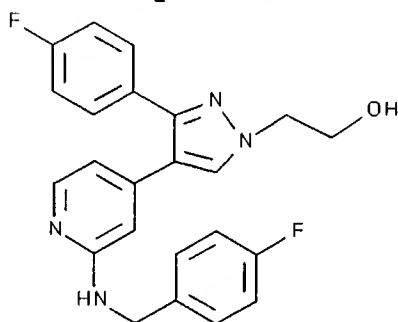
**Example A-287**

N'-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-N,N-dimethyl-1,3-propanediamine

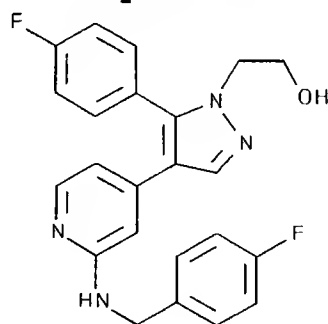
320

**Example A-288**

5-(4-fluorophenyl)-N-2-propynyl-4-(4-pyridinyl)-1H-pyrazol-3-amine

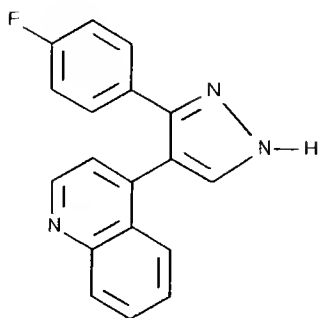
**Example A-289**

3-(4-fluorophenyl)-4-[2-[(4-fluorophenyl)methyl]amino]-4-pyridinyl]-1H-pyrazole-1-ethanol

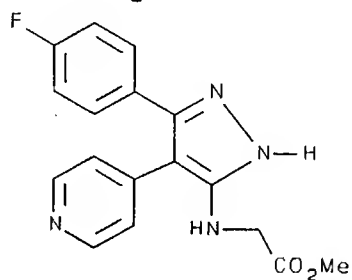
**Example A-290**

5-(4-fluorophenyl)-4-[2-[(4-fluorophenyl)methyl]amino]-4-pyridinyl]-1H-pyrazole-1-ethanol

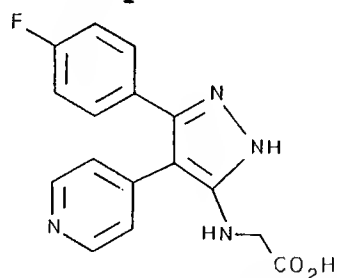
321

**Example A-291**

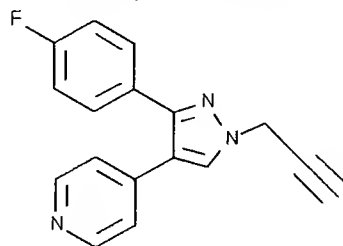
4-[3-[(4-fluorophenyl)-1H-pyrazol-4-yl]quinoline

**Example A-292**

N-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]glycine methyl ester

**Example A-293**

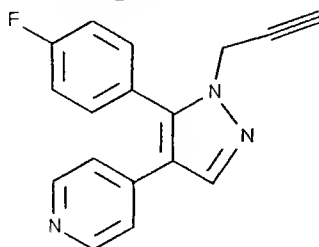
N-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]glycine

**Example A-294**

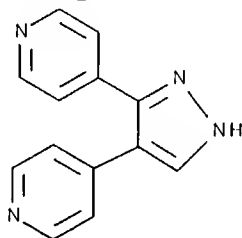


322

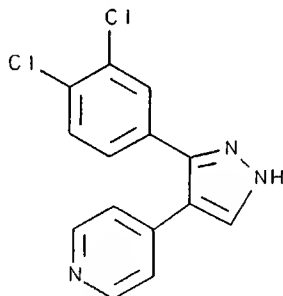
4-[3-(4-fluorophenyl)-1-(2-propynyl)-1H-pyrazol-4-yl]pyridine

**Example A-295**

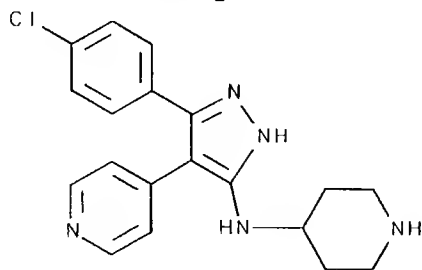
4-[5-(4-fluorophenyl)-1-(2-propynyl)-1H-pyrazol-4-yl]pyridine

**Example A-296**

4,4'-(1H-pyrazole-3,4-diyl)bis[pyridine]

**Example A-297**

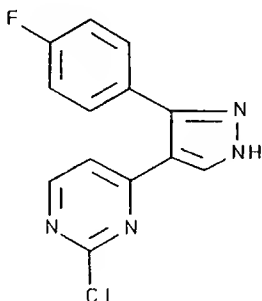
4-[3-(3,4-dichlorophenyl)-1H-pyrazol-4-yl]pyridine

**Example A-298**

N-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-piperidinamine

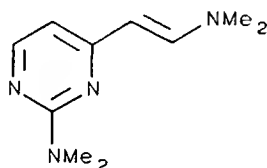
The pyrimidine-substituted compounds of Examples A-299 through A-312 were synthesized in accordance with the chemistry described in Schemes I-XVIII by selection of the corresponding starting reagents:

**Example A-299**



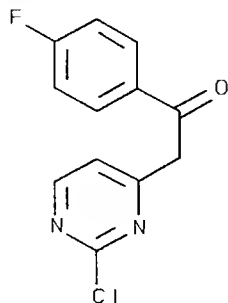
2-Chloro-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]pyrimidine

Step 1:



A mixture of 2,6-dichloro-4-methylpyrimidine (5.0 g, 0.031 mol), triethylamine (6.23 g, 0.062 mol) and catalytic amount of 5% Pd/C in 100 mL of THF was hydrogenated on a Parr apparatus under 40 psi at room temperature. After 0.5 hour, the catalyst was filtered and the filtrate was concentrated. The crude was purified by chromatography on silica gel (ethyl acetate/hexane, 3:7) to give 2.36 g of product as a pale yellow crystal (50% yield); mp: 47-49 °C.

Step 2: Preparation of 2-(2-chloro-4-pyrimidinyl)-1-(4-fluorophenyl)ethanone

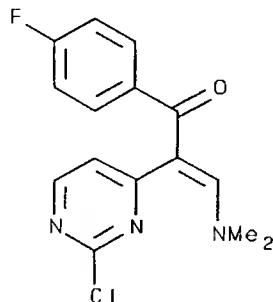


2-(2-chloro-4-pyrimidinyl)-1-(4-fluorophenyl)ethanone

To a solution of lithium diisopropylamide (generated from BuLi (0.045 mol) and diisopropylamine (0.048 mol) in THF) at -78 °C was added a solution of the compound prepared in step 1 (5.5 g, 0.037 mol) in THF slowly over 30 minutes. After 1 hour, a solution of ethyl 4-fluorobenzoate (7.62 g, 0.045 mol) in THF was added and the reaction mixture was stirred overnight and allowed to warm up to room temperature. Water was added and the aqueous phase was extracted with ethyl acetate. Organic layer was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated and the crude product purified by chromatography on silica gel (ethyl acetate/hexane, 3:7) to give 4.78 g of a yellow solid (51% yield), mp: 112-113 °C.

325

Step 3: Preparation of (E)-2-(2-chloro-4-pyrimidinyl)-3-(dimethylamino)-1-(4-fluorophenyl)-2-propen-1-one



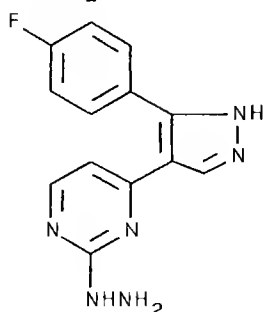
(E)-2-(2-chloro-4-pyrimidinyl)-3-(dimethylamino)-  
1-(4-fluorophenyl)-2-propen-1-one

A mixture of the compound prepared in step 2 (4.7 g, 0.017 mol) in 100 mL of dimethylformamide dimethyl acetal was stirred at room temperature overnight. Excess dimethylformamide dimethyl acetal was removed under vacuum to give 4.5 g of crude product as a thick brown oil, which was used without further purification.

Step 4: Preparation of 2-chloro-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]pyrimidine

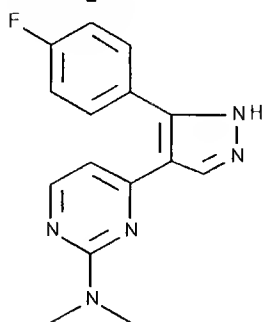
A solution of the compound prepared in step 3 (4.4 g) and hydrazine hydrate (0.82 g, 0.014 mol) was stirred at room temperature for 6 hours. The yellow precipitate was collected by filtration and air-dried to give 1.85 g of 2-chloro-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]pyrimidine as a yellow solid, mp: 204-205 °C; Anal. Calc'd for  $C_{11}H_8ClFN_4$ : C, 56.84; H, 2.94; N, 20.40; Cl, 12.91. Found: C, 56.43; H, 2.76; N, 20.02; Cl, 12.97.

326

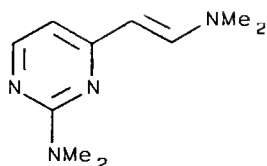
**Example A-300**

4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2(1H)-pyrimidinone hydrazide

A solution of the compound prepared in step 3 of Example A-299 (1.5 g) and hydrazine hydrate (5mL) in ethanol was heated at reflux overnight. After the reaction mixture was cooled, the solvent was removed. The residue was partitioned between ethyl acetate and water. The organic phase was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated and the crude product was purified by recrystallization from ethyl acetate and hexane to give 0.5 g of product, 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2(1H)-pyrimidinone hydrazide, as a pale yellow solid (38% yield), mp: 149-150 °C; Anal. Calc'd for  $C_{13}H_{11}FN_6$ : C, 57.77; H, 4.10; N, 31.10. Found: C, 57.70; H, 4.31; N, 30.73.

**Example A-301**

4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N,N-dimethyl-2-pyrimidinamine

Step 1: Preparation of

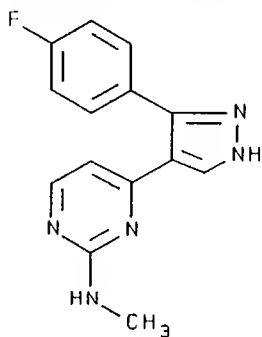
A solution of the compound prepared in step 2 of Example A-299 (3.0 g, 0.02 mol) and *tert*-butylbis(dimethylamino)methane (10.45 g, 0.06 mol) in 40 mL of DMF was stirred at 110 °C overnight. After the solvent was removed under vacuum, water was added and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated and purified by recrystallization from ethyl acetate and hexane to give 1.23 g of a yellow solid product (32% yield), mp: 76-77 °C; Anal. Calc'd for C<sub>10</sub>H<sub>16</sub>N<sub>4</sub>: C, 62.47; H, 8.39; N, 29.14. Found: C, 62.19; H, 8.58; N, 29.02.

Step 2: Preparation of 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N,N-dimethyl-2-pyrimidinamine

To a solution of the compound prepared in step 1 of the present Example (1.2 g, 0.0064 mol) and triethylamine (0.65 g, 0.0064 mol) in 10 mL of toluene was added 4-fluorobenzoyl chloride dropwise. The mixture was heated at reflux for 10 hours and the solvent was removed. The residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated and the crude (1.6 g) was then dissolved in 50 mL of ethanol. The solution was treated with hydrazine hydrate (0.36 g, 0.006 mol) and the mixture was heated at reflux for 2 hours. After ethanol was removed, the residue was partitioned between water and ethyl acetate. The organic phase was washed with brine, dried over magnesium sulfate and filtered. The filtrate was

328

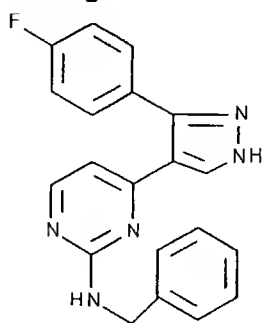
concentrated and the crude was purified by chromatography on silica gel (ethyl acetate/hexane, 1:1) to give 0.6 g of product, 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N,N-dimethyl-2-pyrimidinamine, as a yellow solid (33% yield), mp: 155-156 °C; Anal. Calc'd for  $C_{15}H_{14}FN_5$ : C, 63.59; H, 4.98; N, 24.72. Found: C, 63.32; H, 4.92; N, 24.31.

**Example A-302**

4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N-methyl-2-pyrimidinamine

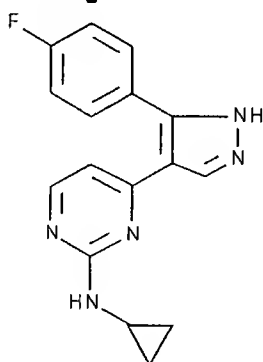
A suspension of 2-chloro-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]pyrimidine prepared in accordance with Example A-299 (0.3 g, 0.0011 mol) in 10 mL of methylamine (40% water solution) was heated in a sealed tube at 100 °C overnight. The mixture was then cooled to room temperature and the precipitate was filtered, air-dried to give 0.2 g of product, 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N-methyl-2-pyrimidinamine, as a white solid (68% yield), mp: 217-218 °C; Anal Calc'd for  $C_{14}H_{12}FN_5$ : C, 62.45; H, 4.49; N, 26.01. Found: C, 62.58; H, 4.36; N, 25.90.

329

**Example A-303**

4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N-(phenylmethyl)-  
2-pyrimidinamine

This compound was synthesized by refluxing 2-chloro-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]pyrimidine prepared in accordance with Example A-299 in benzylamine overnight. The product, 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N-(phenylmethyl)-2-pyrimidinamine, was obtained as a white solid in 95% yield; mp: 216-217 °C; Anal. Calc'd for  $C_{20}H_{16}FN_5$ : C, 69.55; H, 4.67; N, 20.28. Found: C, 69.73; H, 4.69; N, 19.90.

**Example A-304**

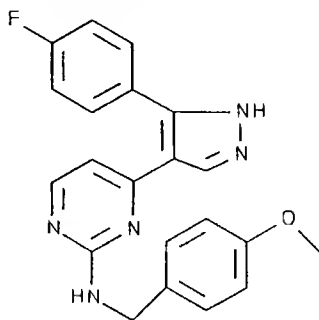
N-cyclopropyl-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyrimidinamine

This compound was synthesized by stirring 2-chloro-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]pyrimidine prepared in accordance with Example A-299 with excess cyclopropylamine in methanol at 50 °C for 12 hours. The



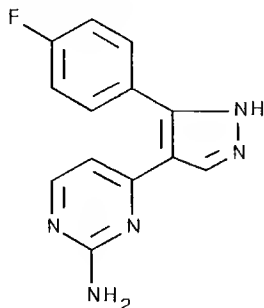
330

product, N-cyclopropyl-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyrimidinamine, was obtained as a white solid in 26% yield, mp: 203-204 °C; Anal. Calc'd for  $C_{16}H_{14}FN_5$ : C, 65.07; H, 4.78; N, 23.71. Found: C, 64.42; H, 4.82; N, 23.58.

**Example A-305**

4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N-[(4-methoxyphenyl)methyl]-2-pyrimidinamine

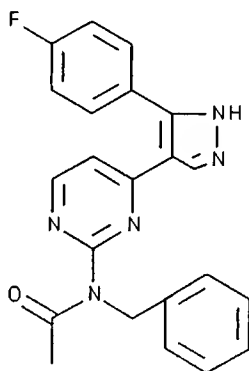
This compound was synthesized by refluxing 2-chloro-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]pyrimidine prepared in accordance with Example A-299 in 4-methoxybenzylamine overnight. The product, 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N-[(4-methoxyphenyl)methyl]-2-pyrimidinamine, was obtained as a off-white solid in 80% yield, mp: 183-185 °C; Anal. Calc'd for  $C_{21}H_{18}FN_5O$ : C, 67.19; H, 4.83, N, 18.66. Found: C, 67.01; H, 5.11; N, 18.93.

**Example A-306**

4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyrimidinamine

331

A solution of 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N-[(4-methoxyphenyl)methyl]-2-pyrimidinamine prepared in accordance with Example A-305 (0.35 g, 0.00093 mol) in 15 mL of trifluoroacetic acid was heated at reflux for 16 hours. Solvent was removed and the residue was partitioned between ethyl acetate and 1 N ammonia hydroxide. Organic layer was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated and purified by chromatography on silica gel (ethyl acetate) to give 0.14 g of product, 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyrimidinamine, as a pale yellow solid (59% yield), mp: 273-274 °C; Anal. Calc'd for  $C_{13}H_{10}FN_5 \cdot 0.25 H_2O$ : C, 60.11; H, 4.07; N, 26.96. Found: C, 60.15; H, 3.82; N, 26.38.

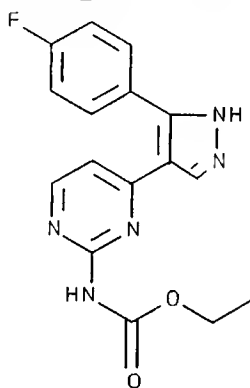
**Example A-307**

N-[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyrimidinyl]-N-(phenylmethyl)acetamide

To a mixture of 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N-(phenylmethyl)-2-pyrimidinamine prepared in accordance with Example A-303 (0.15 g, 0.00043 mol), DMAP (0.027 g, 0.00022 mol) and acetic anhydride (0.066 g, 0.00066 mol) in 10 mL of THF was added triethylamine

332

(0.053 g, 0.00052 mol). The solution was stirred at room temperature overnight. After the removal of solvent, the residue was partitioned between ethyl acetate and water. The organic layer was washed with saturated  $\text{NaHCO}_3$ , washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated and the crude product was triturated with ether to give 0.1 g of product, N-[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyrimidinyl]-N-(phenylmethyl)acetamide, as a white solid (60% yield), mp: 176-178 °C; Anal. Calc'd for  $\text{C}_{22}\text{H}_{18}\text{FN}_5$ : C, 68.21; H, 4.68; N, 18.08. Found: C, 67.67; H, 4.85; N, 17.79.

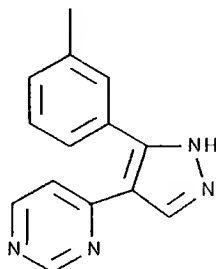
**Example A-308**

Ethyl [4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyrimidinyl]carbamate

To a suspension of 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyrimidinamine prepared in accordance with Example A-306 (0.26 g, 0.001 mol) in 5 mL of pyridine was added ethyl chloroformate dropwise. After the addition, the clear solution was stirred at room temperature for 6 hours. Water was added and the aqueous phase was extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated and the crude was triturated with ether to give 0.15 g of product, ethyl [4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-

333

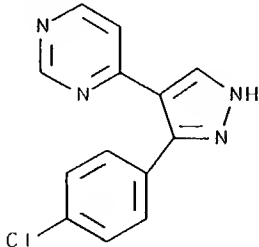
pyrimidinyl]carbamate, as a white solid (46% yield), mp: 163-165 °C; Anal. Calc'd for  $C_{16}H_{14}FN_5O_2$ : C, 58.71; H, 4.31; N, 21.04. Found: C, 59.22; H, 4.51; N, 21.66.

**Example A-309**

4-[3-(3-methylphenyl)-1H-pyrazol-4-yl]pyrimidine

This compound was prepared by the same procedure as described for Example A-208 except that 1-methyl-3-(4'-pyrimidinylacetyl) benzene (prepared as set forth in Step 1 of Example A-19 from 4-methyl-pyrimidine and methyl 3-methylbenzoate) was used in place of 4-fluorobenzoyl-4-pyridinyl methane.

Anal. Calc'd for  $C_{14}H_{12}N_4$  (236.27): C, 71.17; H, 5.12; N, 23.71. Found C, 70.67; H, 5.26; N, 23.53. m.p. (DSC): 151.67 °C.

**Example A-310**

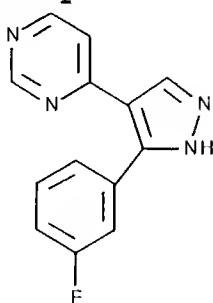
4-[3-(4-chlorophenyl)-1H-pyrazol-4-yl]pyrimidine

This compound was prepared according to the chemistry described in Schemes VI and IX by selection of the corresponding pyrimidine starting material in place

334

of the pyridine starting material.

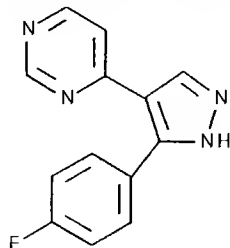
Anal. Calc'd for  $C_{13}H_9N_4Cl \cdot 0.25MH_2O$ : C, 59.78; H, 3.67; N, 21.45. Found: C, 59.89; H, 3.32; N, 21.56. m.p. (DSC): 218.17 °C.

**Example A-311**

4-[3-(3-fluorophenyl)-1H-pyrazol-4-yl]pyrimidine

This compound was prepared according to the chemistry described in Schemes VI and IX by selection of the corresponding pyrimidine starting material in place of the pyridine starting material.

Anal. Calc'd for  $C_{13}H_9N_4F$  (240.24): C, 64.99; H, 3.78; N, 23.22. Found: C, 64.78; H, 3.75; N, 23.31. m.p. (DSC): 168.58 °C.

**Example A-312**

4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]pyrimidine

This compound was prepared according to the chemistry described in Schemes VI and IX by selection of

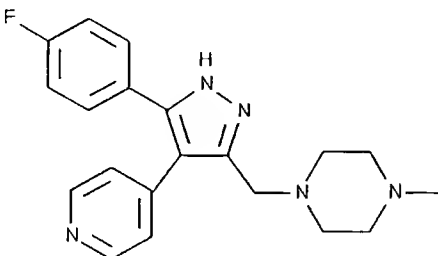
335

the corresponding pyrimidine starting material in place of the pyridine starting material.

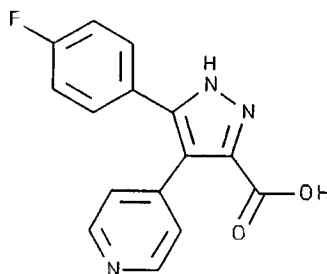
Anal. Calc'd for  $C_{13}H_9N_4F$  (240.24): C, 64.99; H, 3.78; N, 23.32. Found: C, 64.94; H, 3.56; N, 23.44. m.p. (DSC): 191.47 °C.

## Example A-313

The compound 1-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]methyl]-4-methylpiperazine was prepared in  
5 accordance with general synthetic Scheme VII:



Step 1: Preparation of 5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazole-3-carboxylic acid, monohydrate



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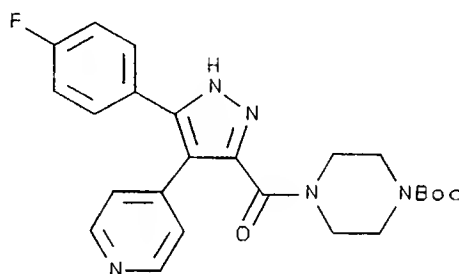
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A mixture of 4-[3-(4-fluorophenyl)-5-methyl-1H-pyrazol-4-yl]pyridine (5.8 g, 24.0909 mmol; prepared as set forth in Example A-4) and potassium permanganate (7.6916 g, 48.1818 mmol) in water (7.5 mL) and *tert*-butanol (10 mL) was heated to reflux at 95 to 100 °C for 6 hours (or until all the potassium permanganate was consumed) and stirred at room temperature overnight. The mixture was diluted with water (150 mL) and filtered to remove manganese dioxide. The aqueous filtrate (pH >10) was extracted with ethyl acetate to remove unreacted starting material. The aqueous layer was acidified with 1N HCl to a pH of about 6.5. A white precipitate was formed. This precipitate was collected by filtration, dried in air, and then dried in a vacuum oven overnight at 50 °C to give 5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazole-3-carboxylic acid, monohydrate (2.7677 g, 40.6 %). The remaining product (0.21 g, 3.1%) was isolated from the

337

mother liquid by reverse phase chromatography. The total isolated yield of 5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazole-3-carboxylic acid, monohydrate was 43.7 %. Anal. Calc'd for  $C_{15}H_{10}N_3FO_2 \cdot H_2O$ : C, 59.80; H, 4.01; N, 13.95; Found: C, 59.48; H, 3.26; N, 13.65. MS ( $MH^+$ ): 284 (base peak).

Step 2: Preparation of 1,1-dimethylethyl 4-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]carbonyl]-1-piperazinecarboxylate



In a solution of 5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazole-3-carboxylic acid, monohydrate (0.9905 g, 3.5 mmol) from step 1 and 1-hydroxybenzotriazole hydrate (0.4824 g, 3.57 mmol) in dimethylformamide (20 mL) at 0 °C under  $N_2$ , 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.6983 g, 3.57 mmol) was added. The solution was stirred at 0 °C under  $N_2$  for 1 hour, then was added 1-tert.-butoxycarbonylpiperazine (0.6585 g, 3.5 mmol) followed by N-methyl morpholine (0.40 mL, 3.6 mmol). The reaction was stirred from 0 °C to room temperature overnight. The reaction mixture was diluted with ethyl acetate and saturated  $NaHCO_3$  solution, extracted. The organic layer was washed with water and brine, and dried over  $MgSO_4$ . After filtration, the solvent was removed under reduced pressure, and crude product was obtained (1.7595 g). The desired product 1,1-dimethylethyl 4-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]carbonyl]-1-piperazinecarboxylate (1.2375 g, 78.4 %) was isolated by chromatography (silica gel, 10:90



isopropyl alcohol/toluene). Anal. Calc'd for  $C_{24}H_{26}N_5FO_3$ : C, 63.85; H, 5.80; N, 15.51; Found: C, 63.75; H, 5.71; N, 15.16. MS ( $MH^+$ ): 452 (base peak).

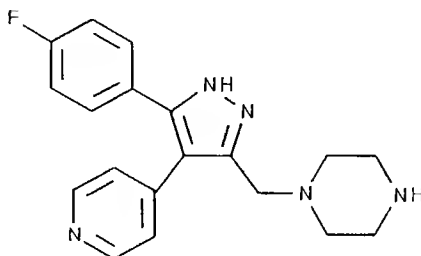
5    Step 3: Preparation of 1-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]methyl]-4-methylpiperazine

To a suspension of 1,1-dimethylethyl 4-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]carbonyl]-1-piperazinecarboxylate (0.451 g, 1.0 mL) in dry tetrahydrofuran (8 mL), 1.0N  $LiAlH_4$  in tetrahydrofuran (2.5 mL, 2.5 mmol) was added dropwise at such a rate as to maintain reflux over 15 minutes. Upon the addition, the suspension became a clear light yellow solution, which was kept boiling for an additional 1.5 hours. Excess  $LiAlH_4$  was decomposed by cautious addition of a solution of KOH (0.5611 g, 10.0 mmol) in water (3.5 mL). Upon hydrolysis, a white salt precipitated. After the addition was completed, the mixture was heated to reflux for 1 hour. The hot solution was filtered by suction through a buchner funnel. Any remaining product was extracted from the precipitate by refluxing with tetrahydrofuran (10 mL) for 1 hour, followed again by suction filtration. The combined filtrates were concentrated under reduced pressure to give a crude residue, which was then diluted with ethyl acetate and washed with water and brine. The organic layer was dried over  $MgSO_4$ . After filtration, the solvent was removed under reduced pressure, and a crude product was obtained. The desired product 1-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]methyl]-4-methylpiperazine (0.1509 g, 50.1 %) was obtained by chromatography (silica gel, 70:30:1 methanol/ethyl acetate/ $NH_4OH$ ). Anal. Calc'd for  $C_{20}H_{22}N_5F \cdot 0.6H_2O$ : C, 66.32; H, 6.46; N, 19.33; Found: C, 66.31; H, 5.96; N, 18.83. MS ( $MH^+$ ): 352 (base peak).

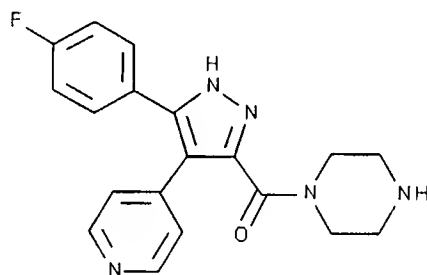
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**Example A-314**

The compound 1-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]methyl]-4-piperazine was prepared in accordance with general synthetic Scheme VII:



Step 1: Preparation of 1-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]carbonyl]piperazine, monohydrate



A solution of 1,1-dimethylethyl 4-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]carbonyl]-1-piperazinecarboxylate (0.6349 g; 1.4077 mmol; prepared as set forth in step 2 of Example A-313) in methylene chloride (3.5 mL) and TFA (1.1 mL, 14.077 mmol) was stirred at room temperature under N<sub>2</sub> for 2 hours. The solvents were removed under reduced pressure, and TFA was chased by methylene chloride and methanol. The resulting colorless oily residue was triturated with methanol. The resulting solid was collected by filtration and dried in a vacuum oven overnight to give the desired product 1-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]carbonyl]piperazine, monohydrate (0.7860 g, 96.4%).

Anal. Calc'd for C<sub>19</sub>H<sub>18</sub>N<sub>5</sub>OF·2TFA·H<sub>2</sub>O: C, 46.24; H, 3.71; N, 11.72; Found: C, 45.87; H, 3.43; N, 11.45. MS (MH<sup>+</sup>): 352

340

(base peak).

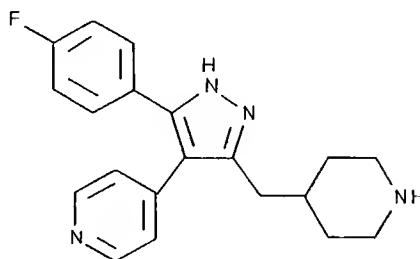
Step 2: Preparation of 1-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]methyl]-4-piperazine

5

By following the method of Example A-313, step 3 and substituting of 1-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]carbonyl]piperazine, monohydrate (prepared in step 1 of this Example) for 1,1-dimethylethyl 4-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]carbonyl]-1-piperazinecarboxylate, the title product 1-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]methyl]-4-piperazine was obtained. Anal. Calc'd for  $C_{19}H_{20}N_5F \cdot 0.75H_2O$ : C, 65.03, H, 6.18, N, 19.96. Found: C, 65.47, H, 5.83, N, 19.35. MS ( $MH^+$ ): 338 (base peak).

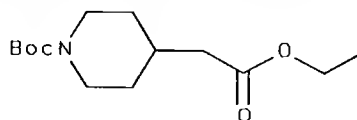
**Example A-315**

20 The compound 4-[3-(4-fluorophenyl)-5-(4-piperidinylmethyl)-1H-pyrazol-4-yl]pyridine was prepared in accordance with general synthetic Scheme XX:



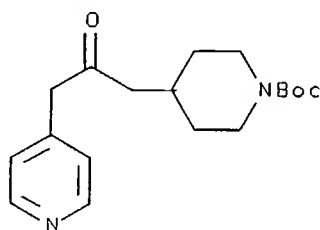
Step 1: Preparation of ethyl 1-[(1,1-dimethylethoxy)carbonyl]-4-piperidineacetate

25



Ethyl 4-pyridyl acetate was converted to 2-(4-piperidinyl) ethyl acetate hydrochloride by hydrogenation (60 psi H<sub>2</sub>) catalyzed by 5% Pt/C at 40 °C in ethanol and HCl solution. To a solution of 2-(4-piperidinyl)ethyl acetate hydrochloride (21.79g, 0.105mol) in tetrahydrofuran (500 mL) at 0 °C, triethylamine (32.06 mL, 0.230 mol) was added followed by di-tert-butylidicarbonate (23.21g, 0.105mol). The reaction mixture was stirred under N<sub>2</sub> from 0 °C to room temperature overnight. After removing tetrahydrofuran, the reaction mixture was diluted with ethanol, washed with saturated NaHCO<sub>3</sub>, 10 % citric acid, water and brine, and dried over MgSO<sub>4</sub>. After filtration, the solvent was removed under reduced pressure. The resulting oily product was dried under vacuum to give ethyl 1-[(1,1-dimethylethoxy)carbonyl]-4-piperidineacetate (27.37 g, 95.9 %). The structure of this product was confirmed by NMR.

Step 2: Preparation of 1,1-dimethylethyl 4-[2-oxo-3-(4-pyridinyl)propyl]-1-piperidinecarboxylate

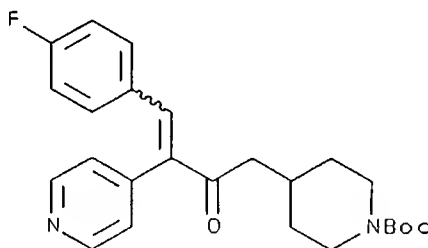


To a solution of diisopropylamide (6.15 mL, 43.91 mmol) in dry tetrahydrofuran (40 mL) at 0 °C was added 2.5 M butyl lithium solution in hexane (16.22 mL, 40.53 mmol) dropwise over 10 minutes. After the addition, the lithium diisopropylamide solution was stirred at 0 °C for 20 minutes, then cooled to -78 °C. 4-Picoline (3.98 mL, 40.53 mmol) was added to the above lithium diisopropylamide solution under N<sub>2</sub> dropwise over 10 minutes. The resulting solution was stirred at -78 °C under N<sub>2</sub> for 1.5 hours, then transferred into a suspension

342

of anhydrous cerium chloride (10.0 g, 40.53 mmol) in tetrahydrofuran (40 mL) at -78 °C under N<sub>2</sub>. The mixture was stirred at -78 °C under N<sub>2</sub> for 2 hours, then a solution of ethyl 1-[(1,1-dimethylethoxy)carbonyl]-4-piperidineacetate (from step 1 of this Example) (10.98 g, 40.53 mmol) in tetrahydrofuran (40 mL) was added slowly for 1 hour. The mixture was stirred under N<sub>2</sub> from -78 °C to room temperature overnight. The reaction was quenched with water, diluted with ethyl acetate, and washed with a pH 7 buffer. The organic layer was washed with water and brine. After filtration, the solvent was removed under reduced pressure to give a crude product mixture. The desired product 1,1-dimethylethyl 4-[2-oxo-3-(4-pyridinyl)propyl]-1-piperidinecarboxylate (3.19 g, 25%) was isolated by chromatography (silica gel, 50:50 - 75:25- 100:0 ethyl acetate/hexane).

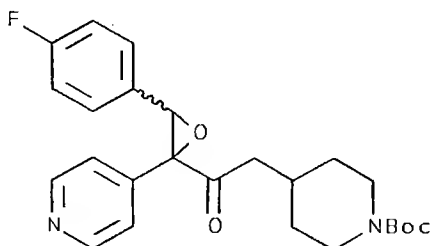
Step 3: Preparation of 1,1-dimethylethyl 4-[4-(4-fluorophenyl)-2-oxo-3-(4-pyridinyl)-3-butenyl]-1-piperidinecarboxylate



1,1-Dimethylethyl 4-[4-(4-fluorophenyl)-2-oxo-3-(4-pyridinyl)-3-butenyl]-1-piperidinecarboxylate was prepared by the same method as described for step 1 of Example A-1 by replacing 4-pyridylacetone and 3-fluoro-p-anisaldehyde with the ketone of step 2 of the present Example and 4-fluorobenzaldehyde, respectively.

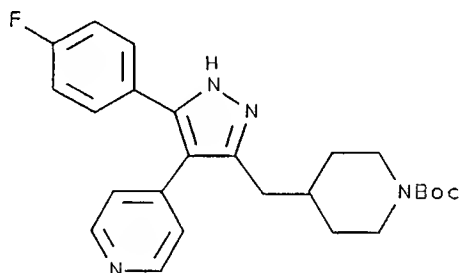
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Step 4: Preparation of 1,1-dimethylethyl 4-[2-[3-(4-fluorophenyl)-2-(4-pyridinyl)oxiranyl]-2-oxoethyl]-1-piperidinecarboxylate



5           1,1-Dimethylethyl 4-[2-[3-(4-fluorophenyl)-2-(4-pyridinyl)oxiranyl]-2-oxoethyl]-1-piperidinecarboxylate was prepared by the same method as described for step 3 of Example A-2 by replacing 4-phenyl-3-(4-pyridyl)-3-butene-2-one with the  $\alpha,\beta$  unsaturated ketone of step 3 of  
10           the present Example.

Step 5: Preparation of 1,1-dimethylethyl 4-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]methyl]-1-piperidinecarboxylate



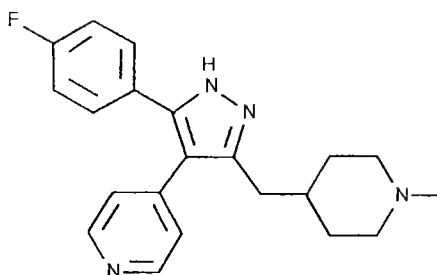
To a solution of 1,1-dimethylethyl 4-[2-[3-(4-fluorophenyl)-2-(4-pyridinyl)oxiranyl]-2-oxoethyl]-1-piperidinecarboxylate prepared in step 4 of this Example  
20           (3.45 g, 7.8409 mmol) in ethanol (15 mL), anhydrous hydrazine (0.50 mL, 15.6818 mmol) was added. The reaction was heated to reflux overnight. The reaction solution was cooled to room temperature and ethanol was  
25           removed under reduced pressure. The resulting residue was taken into ethyl acetate, washed with water and brine, and dried over  $\text{MgSO}_4$ . After filtration the solvent

was removed under reduced pressure. The crude residue was purified by chromatography (silica gel, 2:1 - 1:1 - 1:2 hexane/ethyl acetate) to give 1,1-dimethylethyl 4-  
[[5-(4-fluorophenyl)-4,5-dihydro-4-hydroxy-4-(4-  
5 pyridinyl)-1H-pyrazol-3-yl]methyl]-1-piperidinecarboxylate (1.9187 g, 53.9%). This intermediate (1.8611 g, 4.0993 mmol) was dissolved in dry methylene chloride (40 mL) and treated with Martin sulfurane dehydrating reagent (4.13 g, 6.1490 mmol). The  
10 reaction solution was stirred at room temperature under N<sub>2</sub> overnight, then diluted with ethyl acetate, washed with 1N sodium hydroxide solution, water and brine, dried over MgSO<sub>4</sub>. After filtration the solvents were removed. The resulting crude product mixture was purified by flash  
15 chromatography (silica gel, 2:1 - 1:1 - 1:2 Hexane/ethyl acetate) to give 1,1-dimethylethyl 4-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]methyl]-1-piperidinecarboxylate (0.6964 g, 39 %).

20 Step 6: Preparation of 4-[3-(4-fluorophenyl)-5-(4-piperidinylmethyl)-1H-pyrazol-4-yl]pyridine

4-[3-(4-Fluorophenyl)-5-(4-piperidinylmethyl)-1H-pyrazol-4-yl]pyridine was prepared using the same method  
25 as described for Example A-314, step 1 by replacing 1-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]carbonyl]piperazine, monohydrate with the pyrazole of step 5 of the present Example. Anal. Calc'd for C<sub>20</sub>H<sub>21</sub>N<sub>4</sub>F·2TFA·1.25H<sub>2</sub>O: C, 49.11; H, 4.38; N, 9.54; Found:  
30 C, 48.74; H, 4.02; N, 9.57. MS (MH<sup>+</sup>): 337 (base peak).

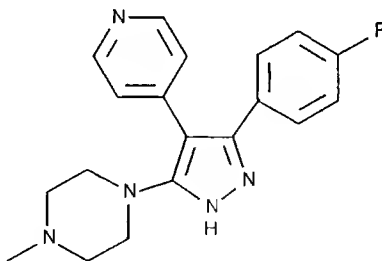
345

**Example A-316**

4-[3-(4-fluorophenyl)-5-[(1-methyl-4-piperidiny)methyl]-  
 5 1H-pyrazol-4-yl]pyridine was prepared by the same method  
 as described for step 3 of Example A-313 by replacing  
 1,1-dimethylethyl 4-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-  
 1H-pyrazol-3-yl]carbonyl]-1-piperazinecarboxylate with  
 the pyrazole of step 5 of the present Example. Anal.  
 10 Calc'd for  $C_{21}H_{23}N_4F \cdot 0.2 H_2O$ : C, 71.24; H, 6.66; N, 15.82;  
 Found: C, 71.04; H, 6.54; N, 15.56. MS ( $MH^+$ ): 351 (base  
 peak).

**Example A-317**

15 The compound 1-[5-(4-fluorophenyl)-4-(4-pyridinyl)-  
 1H-pyrazol-3-yl]-4-methylpiperazine, dihydrate was  
 prepared in accordance with general synthetic Scheme II:



20 2-(4-Pyridyl)-1-(4-fluorophenyl)ethanone  
 hydrochloride (5.9g, 0.023 moles) was dissolved in a  
 methylene chloride/methanol solution (70/15) at room  
 temperature and N-chlorosuccinimide (3.25g, 0.024 moles)  
 was added as a solid. The mixture was stirred at room  
 25 temperature for 2.5 hours.  
 N-methylpiperazinylthiosemicarbazide (4.1g, 0.023 moles)  
 was added as a solid and the mixture was stirred for 3

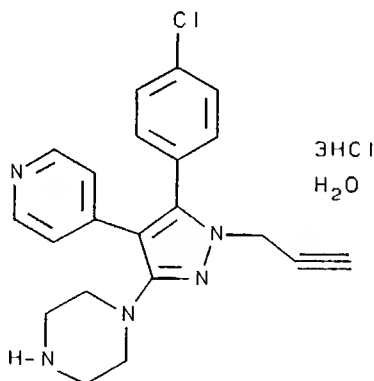


346

days at room temperature. The mixture was diluted with 100 mL of methylene chloride and washed with saturated aqueous sodium bicarbonate solution. The organic phase was dried ( $\text{MgSO}_4$ ) and solvent removed using a rotary evaporator. The residue was treated with ethyl acetate with stirring while cooling in an ice bath. The solid formed was filtered and recrystallized from ethyl acetate with a small amount of methanol to give 1.7g (22%) of 1-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-methylpiperazine, dihydrate. Anal. Calc'd. for  $\text{C}_{19}\text{H}_{20}\text{FN}_5 \cdot 2\text{H}_2\text{O}$ : C, 61.11; H, 6.48; N, 18.75. Found: C, 60.59; H, 6.41; N, 18.44. M.p. (DSC) 262-264 °C;  $\text{MH}^+ = 338$ .

#### Example A-318

The compound 1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1-(2-propynyl)-1H-pyrazol-3-yl]piperazine, trihydrochloride monohydrate was prepared in accordance with general synthetic Scheme VII:



To a mixture of sodium hydride (30 mg, 1.5 mmol) in dimethylformamide (25 mL) stirred under a nitrogen atmosphere at room temperature was added 3-(4-chlorophenyl)-4-(4-pyridyl)-5-(4-N-tert.-butoxycarbonylpiperazinyl)pyrazole (500 mg, 1.1 mmol; prepared as set forth in Example A-169). After stirring for 1 hour, propargyl bromide (225 mg, 1.5 mmol, 80% solution in toluene) was added. After stirring for an

additional 2 hour at room temperature, the reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was dried with  $\text{MgSO}_4$ , filtered and concentrated in vacuo. The residue was

5 chromatographed on silica gel using 70% ethyl acetate/hexane as the eluent to give 110 mg of 3-(4-chlorophenyl)-4-(4-pyridyl)-5-(4-N-tert.-butoxycarbonyl-piperazinyl)pyrazole (24%), m. p. 204-205 °C. Anal. Calc'd. for  $\text{C}_{26}\text{H}_{28}\text{ClN}_5\text{O}_2$ : C, 65.33; H, 5.90; N, 14.65.

10 Found: C, 65.12; H, 5.81; N, 14.70.

A solution of HCl in methanol (5 mL) was generated by addition of acetyl chloride (200 mg) to methanol while cooling (5 °C). 3-(4-Chlorophenyl)-4-(4-pyridyl)-5-(4-N-tert.-butoxycarbonylpiperazinyl)pyrazole (100 mg, 0.2

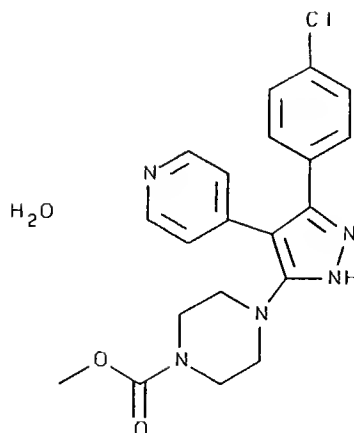
15 mmol) prepared above was added and the reaction stirred in the cold for one hour. The reaction mixture was concentrated in vacuo and the residue azeotroped with toluene to give 100 mg of 1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1-(2-propynyl)-1H-pyrazol-3-yl]piperazine,

20 trihydrochloride monohydrate (90%), m.p.=231-233 °C (dec.). Anal. Calc'd. for  $\text{C}_{21}\text{H}_{20}\text{N}_5\text{Cl}\cdot 3\text{HCl}\cdot \text{H}_2\text{O}$ : C, 49.92; H, 4.99; N, 13.86. Found: C, 49.71; H, 4.89; N, 13.61.

#### Example A-319

25 The compound methyl 4-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1-piperazinecarboxylate, monohydrate was prepared in accordance with general synthetic Scheme II:

348



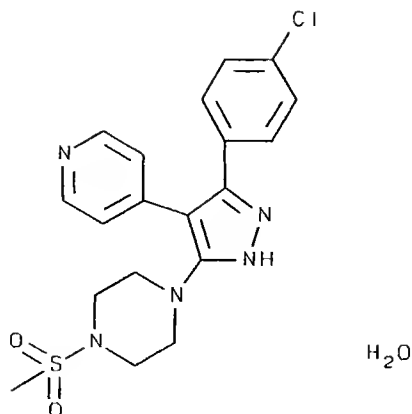
Methyl chloroformate (55 mg) was added to a solution of 3-(4-chlorophenyl)-4-(4-pyridyl)-5-(4-piperazinyl) pyrazole (200 mg, 0.54 mmol; prepared as set forth in  
5 Example A-169) and 4-dimethylaminopyridine (5 mg) in pyridine (10 mL). The mixture was stirred at room temperature for 3 hours. Additional methyl chloroformate (30 mg) was added and stirring was continued for 24  
10 hours. The solvent was removed in vacuo. The residue was treated with water and extracted with ethyl acetate. After drying the organic layer (MgSO<sub>4</sub>), the solvent was blown down to a volume of 10 mL and refrigerated. The resultant crystalline solid was filtered and air dried to  
15 give 103 mg (48%) of methyl 4-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1-piperazinecarboxylate, monohydrate, mp 264-265 °C. Anal. Calc'd. for C<sub>20</sub>H<sub>20</sub>ClN<sub>5</sub>O<sub>2</sub>·H<sub>2</sub>O: C, 57.76; H, 5.33; N, 16.84. Found: C, 57.98; H, 4.89; N, 16.44.

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#### Example A-320

The compound 1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-(methylsulfonyl)piperazine, monohydrate was prepared in accordance with general  
25 synthetic Scheme II:

349

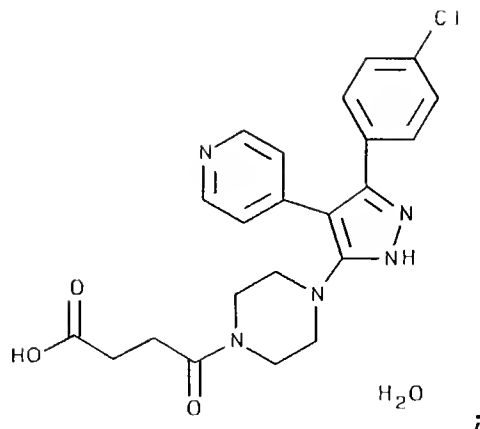


A solution of 3-(4-chlorophenyl)-4-(4-pyridyl)-5-(4-piperazinyl)pyrazole (200 mg; 0.54 mmol; prepared as set forth in Example A-169), methanesulfonyl chloride (75 mg) and 4-dimethylaminopyridine (5 mg) in pyridine was stirred at room temperature for 3 hours. The solvent was removed in vacuo and the residue was treated with water. The resultant crystalline solid was filtered, air dried and recrystallized from methanol and water to give 118 mg (37%) of 1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-(methylsulfonyl)piperazine, monohydrate, m.p. 245-248 °C. Anal. Calc'd. for C<sub>19</sub>H<sub>20</sub>ClN<sub>5</sub>SO<sub>2</sub>·H<sub>2</sub>O: C, 52.35; H, 5.09; N, 16.07. Found: C, 52.18; H, 5.31; N, 16.00.

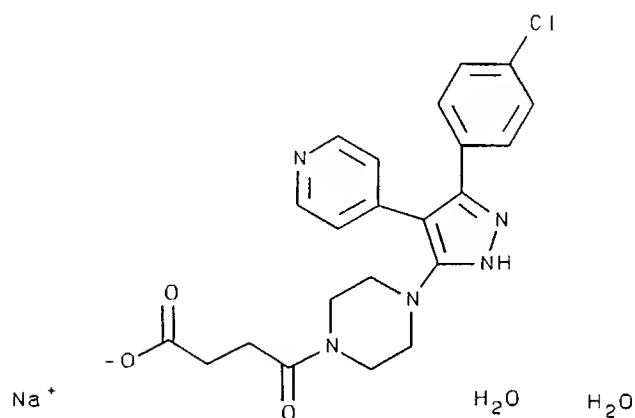
#### Example A-321

The compounds 4-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-γ-oxo-1-piperazinebutanoic acid, dihydrate, and 4-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-γ-oxo-1-piperazinebutanoic acid, monosodium salt dihydrate, were prepared in accordance with general synthetic Scheme II:

350



and



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A solution of 3-(4-chlorophenyl)-4-(4-pyridyl)-5-(4-piperziny)pyrazole (200 mg; 0.54 mmol; prepared as set forth in Example A-169), succinic anhydride (60 mg, 0.55 mmol) and 4-dimethylaminopyridine (5 mg) was stirred at room temperature for 24 hours. The solvent was removed in vacuo and the residue treated with methanol and water (1:1). The resultant crystalline solid was filtered and air dried to give 170 mg (58%) of 4-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]- $\gamma$ -oxo-1-piperazinebutanoic acid, dihydrate, m. p. 281-283 °C (dec.). Anal. Calc'd. for  $\text{C}_{22}\text{H}_{22}\text{ClN}_5\text{O}_3 \cdot 2\text{H}_2\text{O}$ : C, 55.52; H, 5.51; N, 14.72. Found: C, 55.11; H, 5.20; N, 14.44.

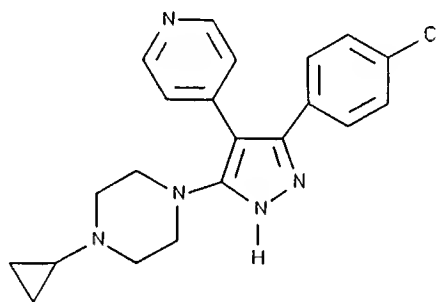
A slurry of 4-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]- $\gamma$ -oxo-1-piperazinebutanoic acid, dihydrate (150 mg, 0.31 mmol) from above in methanol (10 mL) was treated with a solution of sodium hydroxide (12

351

mg, 0.31 mmol) in methanol (2 mL). The reaction was stirred at room temperature for 15 minutes until dissolution was completed. The solvent was removed in vacuo. The residue was treated with tetrahydrofuran and filtered and air dried to give 150 mg (97%) of 4-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]- $\gamma$ -oxo-1-piperazinebutanoic acid, monosodium salt dihydrate as a solid. Anal. Calc'd. for  $C_{22}H_{21}ClN_5O_3Na \cdot 2H_2O$ : C, 53.07; H, 5.06; N, 14.07. Found: C, 52.81; H, 5.11; N, 13.90.

#### Example A-322

The compound 1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-cyclopropylpiperazine was prepared in accordance with general synthetic Scheme II:



To a solution of 3-(4-chlorophenyl)-4-(4-pyridyl)-5-(4-piperazinyl)pyrazole (1.95g; 5.8 mmol; prepared as set forth in Example A-169) and acetic acid (3.6 g, 60 mmol) containing 5A molecular sieves (6 g) was added [(1-ethoxycyclopropyl)oxy]trimethylsilane (6 g, 35 mmol). After stirring for 5 minutes, sodium cyanoborohydride (1.7 g, 26 mmol) was added and the mixture was refluxed under a nitrogen atmosphere for 6 hours. The reaction mixture was filtered hot and the filtrate concentrated in vacuo. Water (50 mL) was added and the solution made basic with 2N sodium hydroxide. The resultant gel was extracted with dichloroethane and the combined organic extracts dried ( $MgSO_4$ ). Evaporation again yielded a gel which was treated with hot methanol. Upon cooling, the product crystallized to give 1.4 g (63%) of 1-[5-(4-

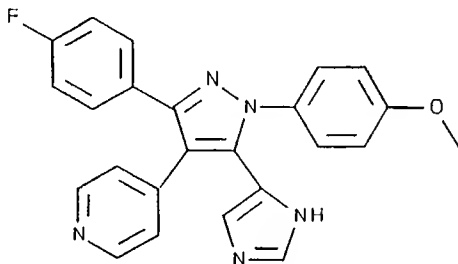
352

chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl)-4-cyclopropylpiperazine, m. p. 264-265 °C. Anal. Calc'd. for  $C_{21}H_{22}ClN_5 \cdot 1.5 H_2O$ : C, 61.99; H, 6.19; N, 17.21. Found: C, 62.05; H, 5.81; N, 16.81.

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**Example A-323**

The compound 4-[3-(4-fluorophenyl)-5-(1H-imidazol-4-yl)-1-(4-methoxyphenyl)-1H-pyrazol-4-yl]pyridine was prepared in accordance with general synthetic Scheme V:



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To a suspension of sodium hydride (1.0 g, 0.025 mol) in 50 mL of dimethylformamide was added methyl 4-imidazolecarboxylate (2.95 g, 0.023 mol) portionwise at room temperature. The mixture was stirred at room temperature for 0.5 hour. Then 2-(trimethylsilyl)ethoxymethyl chloride (4.17 g, 0.025 mol) was added dropwise over 5 minutes. The reaction mixture was stirred for 4 hours and quenched by cautiously adding water. The aqueous phase was extracted with ethyl acetate and the organic layer was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated and the crude was purified by chromatography on silica gel using ethyl acetate/hexane (8:2) as the eluent to give 4.0 g of the major regioisomer as a clear oil.

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To a solution of 4-fluorobenzoyl-4'-pyridyl methane (8.6 g, 0.04 mol, prepared as set forth in Step 1 of Example A-208) in 150 mL of ethanol was added p-methoxyphenylhydrazine hydrochloride (7.34 g, 0.042 mol), followed by triethylamine (4.05 g, 0.04 mol). The reaction mixture was refluxed for 16 hours. After the

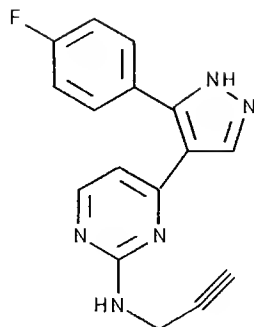
removal of solvent, the residue was partitioned between water and ethyl acetate. The organic layer was washed with brine, dried over  $\text{MgSO}_4$  and filtered. The filtrate was concentrated and the crude residue was purified by  
5 recrystallization from ethyl acetate and hexane to give 8.45 g of the product hydrazone as a yellow solid. To a solution of sodium hexamethyldisilazide (9 mL of 1.0 M tetrahydrofuran solution, 0.009 mol) was added a solution of this hydrazone (1.35 g, 0.004 mol) in 10 mL of dry  
10 tetrahydrofuran at 0 °C. After stirring for 30 minutes at this temperature, a solution of the regioisomer prepared above (1.1 g, 0.0042 mol) in 5 mL of dry tetrahydrofuran was added dropwise. The reaction mixture was stirred for 3 hours at room temperature. Water was  
15 added and the aqueous phase was extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated and the crude product was purified by chromatography on silica gel using ethyl acetate as the  
20 eluent to give 0.74 g of the desired product as an orange solid (34%). Deprotection of the above solid by using tetrabutylammonium fluoride afforded 0.37 g of 4-[3-(4-fluorophenyl)-5-(1H-imidazol-4-yl)-1-(4-methoxyphenyl)-1H-pyrazol-4-yl]pyridine as a yellow solid (75%), mp:  
25 124-126 °C. Anal. Calc'd. for  $\text{C}_{24}\text{H}_{18}\text{FN}_5\text{O} \cdot 0.5 \text{H}_2\text{O}$ : C, 68.56; H, 4.55; N, 16.66. Found: C, 68.44; H, 4.39; N, 16.00.

#### Example A-324

30 The compound 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N-2-propynyl-2-pyrimidinamine was prepared in accordance with general synthetic Scheme XII:



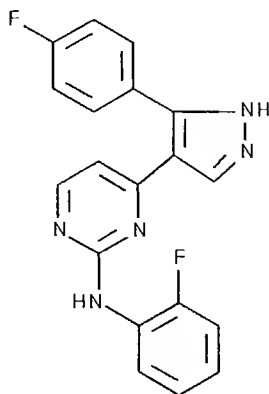
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A mixture of 2-chloro-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]pyrimidine (0.28 g; 0.001 mol; prepared as set forth in Example A-299) and 10 mL propargylamine was heated at reflux for 16 hour. Excess amine was removed in vacuo and the residue was partitioned between water and ethyl acetate. The organic layer was washed with brine, dried over  $\text{MgSO}_4$  and filtered. The filtrate was concentrated and the residue purified by chromatography on silica gel using ethyl acetate/hexane (1:1) as the eluent to give 0.21 g of 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N-2-propynyl-2-pyrimidinamine as a pale yellow solid (68% yield), mp: 186-187 °C. Anal. Calc'd. for  $\text{C}_{16}\text{H}_{12}\text{FN}_5$ : C, 65.52; H, 4.12; N, 23.88. Found: C, 64.99; H, 4.15; N, 23.91.

#### Example A-325

The compound N-(2-fluorophenyl)-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyrimidinamine was prepared in accordance with general synthetic Scheme XII:

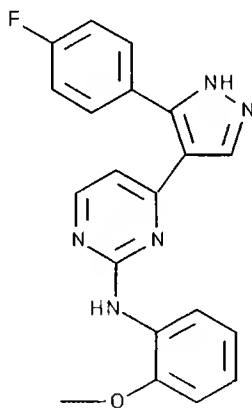


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A mixture of 2-chloro-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]pyrimidine (0.37 g; 0.0013 mol; prepared as set forth in Example A-299), 7 mL of 2-fluoroaniline and 2 drops of methanol was heated at 180 °C in a sealed tube for 16 hours. Excess amine was removed by vacuum distillation and the residue was treated with ethyl acetate to give 0.35 g of N-(2-fluorophenyl)-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyrimidinamine as a yellow solid (77%), mp: 239-240 °C. Anal. Calc'd. for  $C_{19}H_{13}F_2N_5$ : C, 65.33; H, 3.75; N, 20.05. Found: C, 64.95; H, 3.80; N, 19.77.

#### Example A-326

The compound 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N-(2-methoxyphenyl)-2-pyrimidinamine was prepared in accordance with general synthetic Scheme XII:

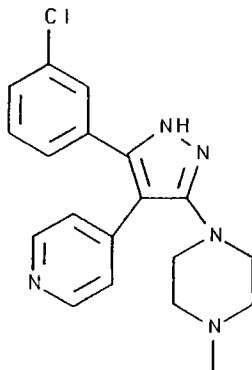


4-[3-(4-Fluorophenyl)-1H-pyrazol-4-yl]-N-(2-methoxyphenyl)-2-pyrimidinamine was synthesized in 41% yield using the same method described for the preparation of N-(2-fluorophenyl)-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyrimidinamine in Example A-325 using 2-methoxyaniline in place of 2-fluoroaniline; mp: 265 °C (dec.). Anal. Calc'd. for  $C_{20}H_{16}FN_5O$ : C, 66.47; H, 4.46; N, 19.38. Found: C, 66.70; H, 4.53; N, 19.20.

356

**Example A-327**

The compound 1-[5-(3-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-methylpiperazine was prepared in accordance with general synthetic Scheme II:



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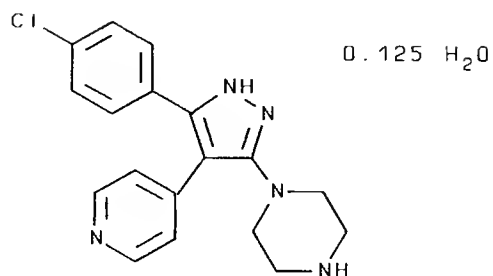
1-[5-(3-Chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-methylpiperazine was synthesized in 12% yield as a pale yellow solid using the same method described for the preparation of 1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-methylpiperazine in Example A-170 using 2-(4-pyridyl)-1-(3-chlorophenyl)ethanone in place of 2-(4-pyridyl)-1-(4-chlorophenyl)ethanone; mp: 229-231 °C. Anal. Calc'd. for  $C_{19}H_{20}ClN_5 \cdot 0.4 H_2O$ : C, 63.21; H, 5.81; N, 19.40. Found: C, 62.85; H, 5.57; N, 19.77.

Additional aminopyrazole compounds that were synthesized in accordance with the chemistry described in Scheme II by selection of the corresponding starting reagents include the compounds disclosed in Table 3-1 below.

TABLE 3-1

	EXAMPLE	FORMULA	MW	Theoretical			Found			DSC (mp)
				C	H	N	C	H	N	
5	A-328	C <sub>18</sub> H <sub>18</sub> ClN <sub>5</sub> ·1/8H <sub>2</sub> O	342.08	63.20	5.30	20.47	63.04	5.36	20.33	199°C
	A-329	C <sub>23</sub> H <sub>33</sub> ClN <sub>6</sub> O <sub>2</sub>	533.08	65.34	6.24	15.77	64.98	6.11	15.58	(168-171°C)
	A-330	C <sub>23</sub> H <sub>25</sub> ClN <sub>5</sub> O <sub>2</sub>	457.94	60.33	5.50	15.29	59.97	5.52	15.17	(253-255°C)
	A-331	C <sub>22</sub> H <sub>24</sub> ClN <sub>5</sub> O <sub>2</sub>	425.92	62.04	5.68	16.44	61.64	5.94	16.29	(273-275°C)
10	A-332	C <sub>19</sub> H <sub>23</sub> Cl <sub>4</sub> N <sub>5</sub> ·H <sub>2</sub> O	481.26	47.42	4.82	14.35	47.66	5.11	13.74	(217-219°C)
	A-333	C <sub>21</sub> H <sub>20</sub> ClN <sub>5</sub> ·2.5H <sub>2</sub> O	422.92	59.64	4.77	16.56	59.67	4.88	15.96	(247°C) (d)
	A-334	C <sub>20</sub> H <sub>22</sub> ClN <sub>5</sub> ·1/4H <sub>2</sub> O	372.39	64.51	5.96	18.81	64.79	5.97	18.95	242°C
	A-335	C <sub>24</sub> H <sub>22</sub> ClN <sub>5</sub> ·3/4H <sub>2</sub> O	429.44	67.13	5.16	16.31	67.04	5.31	16.32	230°C
	A-336	C <sub>25</sub> H <sub>24</sub> ClN <sub>5</sub> O·1/4H <sub>2</sub> O	450.46	66.66	5.37	15.55	66.64	5.11	15.69	(270-271°C)
	A-337	C <sub>22</sub> H <sub>24</sub> FN <sub>5</sub> O <sub>2</sub> ·H <sub>2</sub> O	427.48	61.81	5.66	16.38	61.88	5.96	16.41	249°C
15	A-338	C <sub>20</sub> H <sub>22</sub> FN <sub>5</sub> ·1/2H <sub>2</sub> O	360.44	66.65	6.15	19.43	66.74	6.59	19.37	241°C
	A-339	C <sub>19</sub> H <sub>20</sub> FN <sub>5</sub> ·3HCl·1/2H <sub>2</sub> O	455.79	50.07	5.09	15.30	49.87	5.47	15.30	(237-239°C)

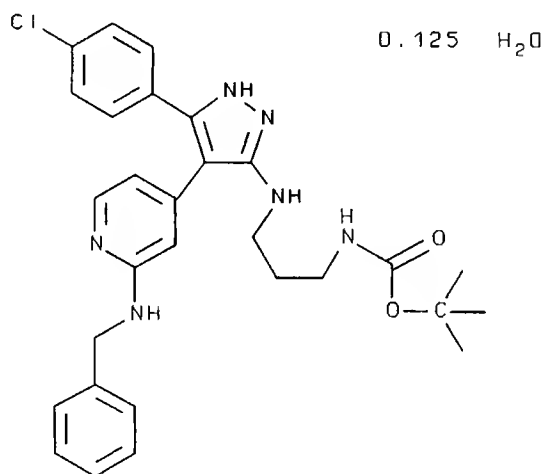
358

**Example A-328**

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1 - [5 - (4-chlorophenyl) - 4 - (4-pyridinyl) - 1H-pyrazol - 3 -  
yl]piperazine

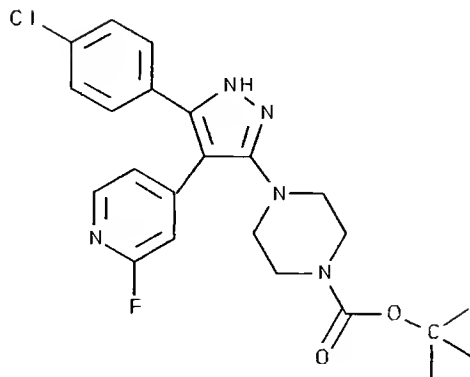
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**Example A-329**

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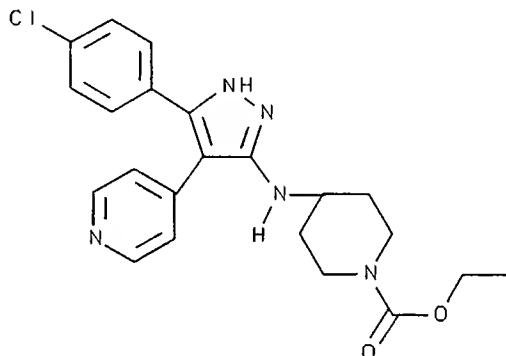
1,1-dimethylethyl [3 - [[5 - (4-chlorophenyl) - 4 - (2 -  
[(phenylmethyl) amino] - 4 - pyridinyl - 1H-pyrazol - 3 -  
yl] amino] propyl] carbamate

359

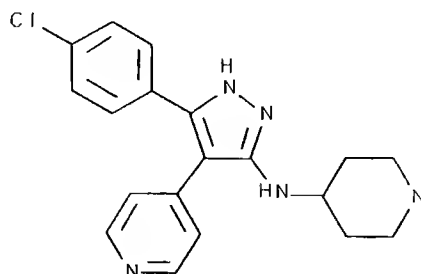
**Example A-330**

5           1,1-dimethylethyl 4-[5-(4-chlorophenyl)-4-(2-fluoro-  
4-pyridinyl)-1H-pyrazol-3-yl]-1-piperazinecarboxylate

10

**Example A-331**

15           ethyl 4-[[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-  
pyrazol-3-yl]amino]-1-piperidinecarboxylate

**Example A-332**

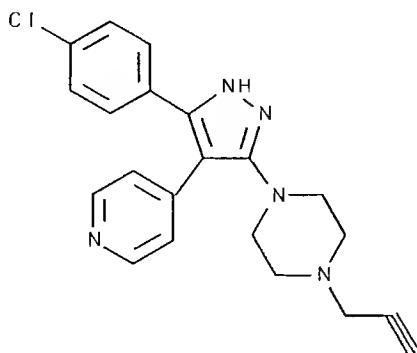
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360

N-[5-(4-chlorophenyl)-4-(4-pyridinyl)-3H-pyrazol-3-yl]-4-piperidineamine, trihydrochloride, monohydrate

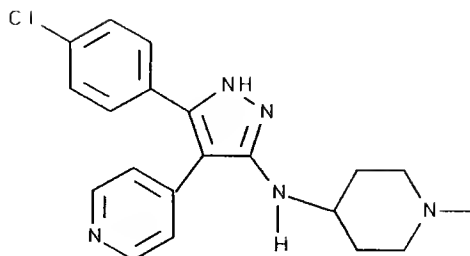
**Example A-333**

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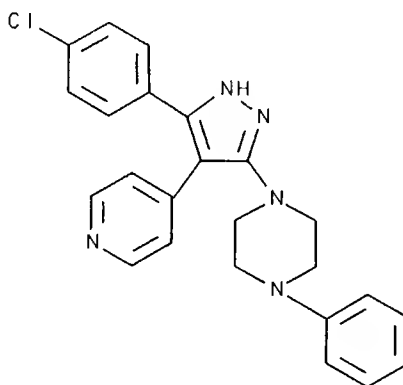


The compound 1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-(2-propynyl)piperazine was prepared in accordance with general synthetic Scheme II. To a suspension of 1-[5-(4-Chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]piperazine (92 mg, 0.27 mmole) in 2 mL of dimethylformamide was added 75 mg (0.54 mmole) of anhydrous potassium carbonate and then 60 microliters of 80% propargyl bromide solution in toluene (containing 64 mg, 0.54 mmole). The resulting mixture was stirred for 30 minutes and then partitioned between ethyl acetate and water. The aqueous layer was further extracted with ethyl acetate, and the combined organic extracts filtered through silica gel using 10% methanol-ethyl acetate as eluent to give, after evaporation of the appropriate fractions, 34 mg of 1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-(2-propynyl)piperazine as a pale yellowish solid, m.p. 247 °C (decomp.). Anal. Calc'd. for  $C_{21}H_{20}ClN_5 \cdot 2.5H_2O$  (MW 422.92): C, 59.64, H, 4.77, N, 16.56. Found: C, 59.67, H, 4.88, N, 15.96.

361

**Example A-334**

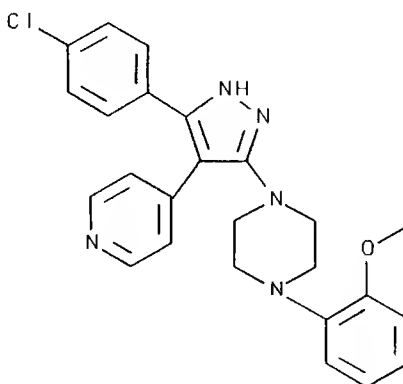
5           N-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1-methyl-4-piperidinamine

**Example A-335**

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1- [5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-phenylpiperazine

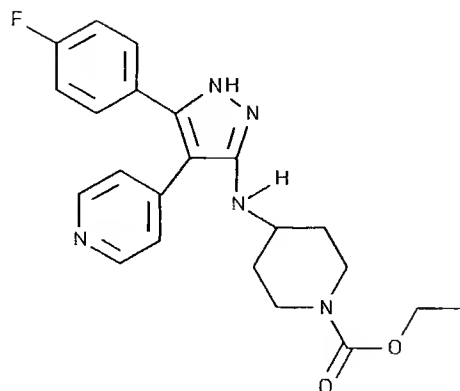
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**Example A-336**

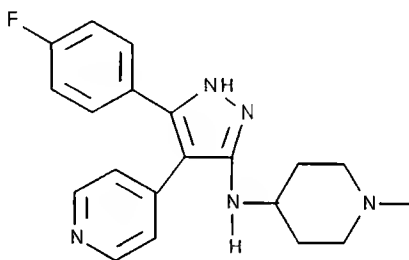
20           1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-(2-methoxyphenyl)piperazine



362

**Example A-337**

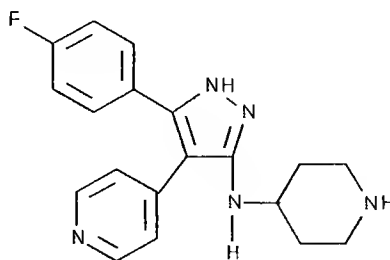
5            Ethyl 4-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]amino]-1-piperidinecarboxylate, monohydrate

**Example A-338**

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N-[5-(4-fluorophenyl)-4-(pyridinyl)-1H-pyrazol-3-yl]-1-methyl-4-piperidinamine

15

**Example A-339**

20            N-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-piperidinamine, trihydrochloride

**Example A-340**

The compound of Example A-170 was also synthesized in the following manner. 1-[5-(4-Chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]piperazine (12.2g, 36 mmol, prepared as set forth in Example A-169), 88% formic acid (20 mL), and formaldehyde (37% formalin solution; 44g, 540 mmol) were combined and stirred at 60 °C for 16 hours under a nitrogen atmosphere. Excess solvent was removed on the rotary evaporator and the residue was dissolved in water (150 mL). The pH was adjusted to 8-9 by addition of solid sodium bicarbonate. The resulting precipitate was filtered and air dried. It was then treated with hot methanol (400 mL), filtered and blown down to a volume of 75 mL, cooled and filtered. After drying in a vacuum oven at 80 °C overnight, there was obtained 8.75g (68%) of 1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-methylpiperazine, m. p. 262-264 °C. Anal. Calc'd. for  $C_{19}H_{20}N_5Cl$ : C, 64.49; H, 5.70; N, 19.79. Found: C, 64.04; H, 5.68; N, 19.63.

The compounds of Examples A-341 through A-345 were synthesized, for example, in accordance with the chemistry described in Scheme XXI by selection of the corresponding starting reagents.

**Example A-341**

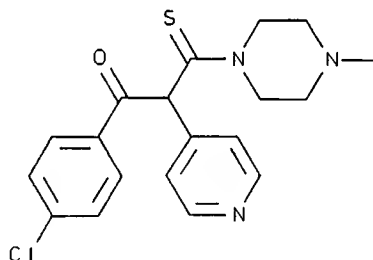
The compound of Example A-170 was also synthesized in the following manner:

Step 1: Preparation of 1-(4-chlorophenyl)-2-(1,3-dithietan-2-ylidene)-2-(4-pyridinyl)ethanone

To a solution of 2-(4-pyridyl)-1-(4-chlorophenyl)ethanone (70.0 g, 0.3 mol) prepared in a similar manner as the compound of Step 1 of Example A-19, dibromomethane (200 mL) and carbon disulfide (25.9 g, 0.34 mol) in acetone (800 mL) was added potassium

carbonate (83.0 g, 0.6 mol). The reaction mixture was stirred at room temperature for 24 hours. An additional two equivalents of potassium carbonate and one equivalent of carbon disulfide was added and the stirring was continued for another 24 hours. Solvent was removed and the residue was partitioned between dichloromethane and water. The organic layer was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated and the crude was stirred with 1000 mL of a mixture of ethyl acetate and ether (1:9) to give 78.4 g of pure product, 1-(4-chlorophenyl)-2-(1,3-dithietan-2-ylidene)-2-(4-pyridinyl)ethanone, as a yellow solid (82%), mp: 177-179 °C. Anal. Calc'd. for  $C_{15}H_{10}ClNOS_2$ : C, 56.33; H, 3.15; N, 4.38. Found: C, 55.80; H, 2.84; N, 4.59.

Step 2: Preparation of 1-[3-(4-chlorophenyl)-3-oxo-2-(4-pyridinyl)-1-thiopropyl]-4-methylpiperazine

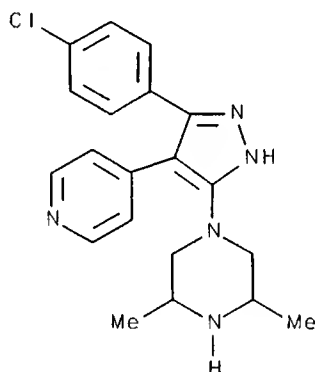


A mixture of 1-(4-chlorophenyl)-2-(1,3-dithietan-2-ylidene)-2-(4-pyridinyl)ethanone (78.3 g, 0.24 mol) and 1-methylpiperazine (75.0 g, 0.73 mol) in 800 mL of toluene was heated at reflux for 2 hours. Solvent and excess 1-methylpiperazine was removed under vacuum and the residue was triturated with a mixture of ethyl acetate and ether (1:3) to give 53.0 g of product, 1-[3-(4-chlorophenyl)-3-oxo-2-(4-pyridinyl)-1-thiopropyl]-4-methylpiperazine, as yellow crystals (60%), mp: 149-151 °C. Anal. Calc'd. for  $C_{19}H_{20}ClN_3OS$ : C, 61.03; H, 5.39; N, 11.24. Found: C, 60.74; H, 5.35; N, 11.14.

Step 3: Preparation of 1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-methylpiperazine

To a suspension of 1-[3-(4-chlorophenyl)-3-oxo-2-(4-pyridinyl)-1-thiopropyl]-4-methylpiperazine (52.0 g, 0.14 mol) in 500 mL of dry tetrahydrofuran was added anhydrous hydrazine (8.9 g, 0.28 mol) dropwise. The reaction mixture was stirred at room temperature for 16 hours. The pale yellow precipitate was filtered and recrystallized from hot methanol to give 30.2 g of 1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-methylpiperazine as a white powder (60%), mp: 267-268 °C. Anal. Calc'd. for  $C_{19}H_{20}ClN_5$ : C, 64.49; H, 5.70; N, 19.79. Found: C, 64.89; H, 5.55; N, 19.99.

**Example A-342**

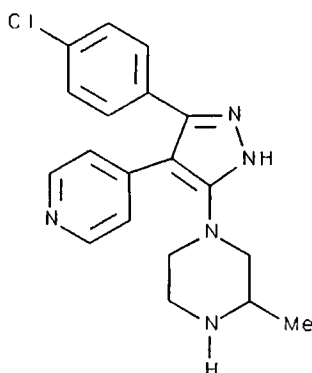


1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-3,5-dimethylpiperazine

A mixture of 1-(4-chlorophenyl)-2-(1,3-dithietan-2-ylidene)-2-(4-pyridinyl)ethanone (3.2 g, 0.01 mol; prepared as set forth in Step 1 of Example A-341) and 2,6-dimethylpiperazine (3.43 g, 0.03 mol) in 35 mL of toluene was heated at reflux for 12 hours. Toluene and excess 2,6-dimethylpiperazine were then removed under vacuum and the crude thiamide produced was used without purification. A solution of the crude thiamide and

366

anhydrous hydrazine (0.65 g, 0.02 mol) in 40 mL of dry tetrahydrofuran was stirred at room temperature overnight. After the removal of tetrahydrofuran, the residue was stirred with a mixture of ethyl acetate and ammonium hydroxide for one hour. The precipitate was filtered and air dried to give 1.6 g of 1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-3,5-dimethylpiperazine as a white solid (43% overall yield), mp: 236-238°C. Anal. Calc'd. for  $C_{20}H_{22}ClN_5 \cdot 0.25H_2O$ : C, 64.51; H, 6.09; N, 18.81; Cl, 9.52. Found: C, 64.28; H, 5.85; N, 18.70; Cl, 9.67.

**Example A-343**

1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-3-methylpiperazine

1-[5-(4-Chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-3-methylpiperazine was prepared according to the same procedure set forth above in Example A-342 except that 2-methylpiperazine was used in place of 2,6-dimethylpiperazine (4% overall yield), mp: 235-237°C.

Anal. Calc'd. for  $C_{19}H_{20}ClN_5 \cdot 0.75H_2O$ : C, 62.12; H, 5.90; N, 19.06. Found: C, 62.23; H, 5.53; N, 18.80.

**Example A-344**

The compound of Example A-317 was also synthesized in the following manner:

Step 1: Preparation of 1-(4-pyridyl)-1-(methylenedithioketene)-2-(4-fluorophenyl)-ethanone

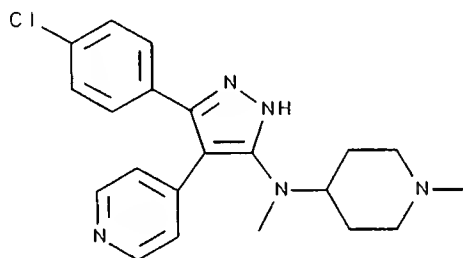
To a solution of 4-fluorobenzoyl-4'-pyridyl methane  
5 (70.0 g, 0.3 mol, prepared as set forth in Step 1 of  
Example A-208) and dibromomethane (125 mL) was added  
solid anhydrous potassium carbonate (55.0 g, 0.4 mol)  
portionwise over five minutes. Carbon disulfide (17 g,  
0.22 mol) was added dropwise over 15 minutes at room  
10 temperature. After stirring for 16 hours under a  
nitrogen atmosphere, the reaction was incomplete.  
Additional carbon disulfide (15 g) was added and the  
reaction mixture was stirred for an additional 24 hours.  
The reaction mixture was filtered and the potassium  
15 carbonate was washed on the filter with methylene  
chloride. The filtered solid was dissolved in water and  
extracted with methylene chloride. The extract was  
combined with the filtrate and dried over magnesium  
sulfate. The drying agent was filtered and the filtrate  
20 concentrated in vacuo. The residue was treated with  
ethyl acetate/ether (1:1), filtered and air dried to give  
1-(4-pyridyl)-1-(methylenedithioketene)-2-(4-  
fluorophenyl)-ethanone (26 g, 86%) as a solid, m.p. 182-  
183 °C; Anal. Calc'd. for  $C_{15}H_{10}FNOS_2$ : C, 59.39; H, 3.32;  
25 N, 4.62. Found: C, 59.18; H, 3.41; N, 4.49.

Step 2: Preparation of 1-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-methylpiperazine, dihydrate

30 A mixture of the 1-(4-pyridyl)-1-(methylenedithioketene)-2-(4-fluorophenyl)-ethanone (3 g,  
0.01 mol) prepared in Step 1 and 1-methylpiperazine (3 g,  
0.03 mol) in 30 mL of toluene was refluxed under a  
nitrogen atmosphere for three hours. The mixture was  
35 cooled and solvent was removed under vacuum. The residue  
was dissolved in dry tetrahydrofuran (30 mL) and

368

anyhydrous hydrazine (640 mg, 0.02 mol) was added. The reaction mixture was stirred at room temperature for 16 hours and the resulting precipitate was filtered. The precipitate was warmed in methanol and a few drops of concentrated ammonium hydroxide were added. The mixture was filtered hot and the filtrate blown down to half the volume. As the filtrate cooled, a product crystallized and was filtered to give 1.5 g (42%) of 1-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-methylpiperazine, dihydrate, mp: 238-240 °C; Anal. Calc'd. for  $C_{19}H_{20}FN_5 \cdot 2H_2O$ : C, 61.11; H, 65.48; N, 18.75. Found: C, 60.79; H, 6.21; N, 18.98.

**Example A-345**

N-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-N,1-dimethyl-4-piperidinamine, dihydrate

**Step 1: Preparation of 1-methyl-4-methylaminopiperidine**

A mixture of 1-methyl-4-piperidone (20 g, 0.18 mol) in methanol:tetrahydrofuran (100 mL, 1:1) and methyl amine (2 M in tetrahydrofuran, 3 mole excess) was placed in a Parr shaker with 5% Pd/C and hydrogenated for two hours at 60 psi and 70°C. The catalyst was filtered and the filtrate concentrated on the rotary evaporator. The crude material was distilled at 44-45°C at 0.3 mm Hg to give 20 g (87%) of 1-methyl-4-methylaminopiperidine. Anal. Calc'd for  $C_7H_{16}N_2$ : C, 65.57; H, 12.58; N, 21.85. Found: C, 65.49; H, 12.44; N: 21.49.

Step 2: Preparation of N-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-N,1-dimethyl-4-piperidinamine, dihydrate

5

A solution of 1-(4-chlorophenyl)-2-(1,3-dithietan-2-ylidene)-2-(4-pyridinyl)ethanone (3.2 g, 0.01 mol; prepared as set forth in Step 1 of Example A-341) and 1-methyl-4-methylaminopiperidine (3.8 g, 0.03 mol) in 30 mL of toluene refluxed for six hours under nitrogen. The mixture was cooled and solvent was removed under vacuum. The residue was dissolved in dry tetrahydrofuran (30 mL) and anhydrous hydrazine (650 mg, 0.02 mol) was added. The reaction mixture was stirred at room temperature under nitrogen for 16 hours. The resulting precipitate was filtered and warmed in methanol and a few drops of concentrated ammonium hydroxide. The mixture was filtered hot and the filtrate blown down to half the volume. As the filtrate cooled, a product separated and was filtered to give 395 of pure N-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-N,1-dimethyl-4-piperidinamine, dihydrate, m.p. 260-261°C. Anal. Calc'd for  $C_{21}H_{24}ClN_5 \cdot 2H_2O$ : C, 60.35; H, 6.75; N, 16.76. Found: C, 59.89; H, 6.56; N: 16.40.

Additional compounds of the present invention that were prepared according to one or more of above reaction schemes (particularly Schemes IX through XVIII) are disclosed in Table 3-2. The specific synthesis scheme or schemes as well as the mass spectroscopy and elemental analysis results for each compound also are disclosed in Table 3-2.



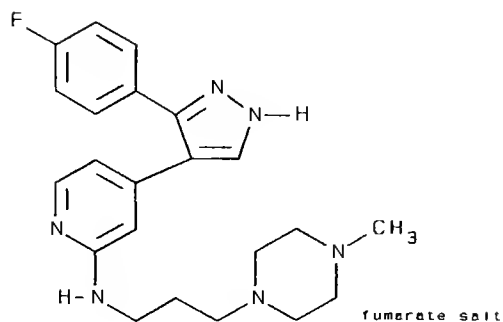
TABLE 3-2

Example	General	MS	Microanalysis											
			M+	C Found	C Found	H Calc	H Found	N Calc	N Found	Water Added	EtOAc Added	CHCl <sub>3</sub> Added	Toluene Added	HCl Added
A-346	XII													
A-347	XII	329	59.33	59.59	5.65	5.47	15.55	15.41	0.8	0.2				
A-348	XII	439	68.46	66.59	8.04	8.48	19.16	16.17						
A-349	XII	397	61.85	61.99	7.79	7.52	17.45	17.39	1.3	0.7				
A-350	XII	449	66.29	66.75	7.60	7.68	17.84	17.00	1.25					
A-351	XII	352	68.36	57.51	6.31	7.31	19.93	17.17						
A-352	XII	366	69.02	66.27	6.62	6.59	19.16	18.22						
A-353	XII	430	69.26	71.50	7.40	6.91	18.36	14.87						
A-354	XII	355	70.48	70.12	6.80	7.15	13.99	13.91				0.5		
A-355	XII	341	66.73	67.09	6.29	6.77	16.04	15.78		0.1				
A-356	XVII	410	63.42	63.61	6.00	6.06	16.81	16.63	0.4					
A-357	XVII	392	54.37	53.93	5.91	6.32	13.78	14.68	0.4					
A-358	XII	394	70.20	68.50	7.17	7.68	17.80	16.58						
A-359	XVII	396	69.21	69.33	7.68	8.01	17.55	17.61	0.2					
A-360	XVII	366	50.81	50.74	5.97	5.80	14.11	14.00	1.2					3
A-361	XII	389	71.12	68.67	5.45	5.64	14.42	12.90						
A-362	XII	375	70.57	68.54	5.12	5.39	14.96	13.90						
A-363	XII	389	71.12	68.86	5.45	5.58	14.42	13.09						
A-364	XVII	368	68.31	68.39	7.15	7.49	18.97	18.93	0.1					
A-365	XVII	338	48.72	48.57	5.47	5.45	14.95	14.79	1.2					3
A-366	XII	397	56.34	56.21	7.31	7.03	17.92	17.89	2					1

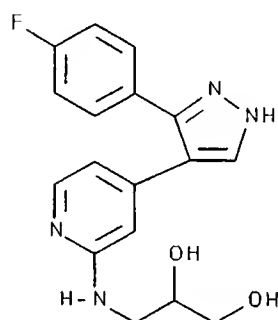
371

A-367	XVII	321	70.25	69.83	5.43	5.62	17.25	17.82	0.25			
A-368	XII	313	64.66	64.28	5.73	5.62	16.76	16.93		0.25		
A-369	XII	412	66.76	66.60	7.36	7.61	16.93	16.74	0.1			
A-370	XII	313	64.66	64.36	5.73	5.59	16.76	16.82		0.25		
A-371	XVII		63.78	63.63	6.37	6.09	17.71	17.24	1			
A-372	XII		68.63	68.80	7.26	7.53	17.40	17.14	0.5			
A-373	XVII	389	58.10	57.99	5.00	4.88	17.83	17.48	0.25			
A-374	XII	354	67.97	67.23	6.84	6.81	19.81	19.38				
A-375	XII	366	68.18	68.06	6.67	6.80	18.93	18.56	0.25			
A-376	XII	375	70.57	68.19	5.12	6.06	14.96	13.13				
A-377	XII	396	64.14	64.44	6.99	6.78	16.02	16.02		0.35		
A-378	XVII	337	66.42	66.44	5.22	4.91	16.31	16.27	0.4			
A-379	XVII	339	62.76	62.80	6.04	5.43	15.41	15.17	1.4			
A-380	XVII	381	63.31	63.40	5.19	5.82	14.06	13.84	1			1
A-381	XVII	307	70.57	69.69	4.94	5.00	18.29	17.68				
A-382	XVII											
A-383	XVII											
A-384	320	55.4 8	53.44	5.64	5.00	17.03	21.60					
A-385	XI	280	52.65	52.51	5.98	5.17	10.83	11.12				1
A-386	XII	351	64.96	64.77	5.82	5.34	14.85	15.03	1	0.1		
A-387	XII	353	65.29	65.62	6.32	6.14	14.64	14.47	0.7	0.2		
A-388		394	54.93	55.34	6.21	6.79	13.93	14.01				3

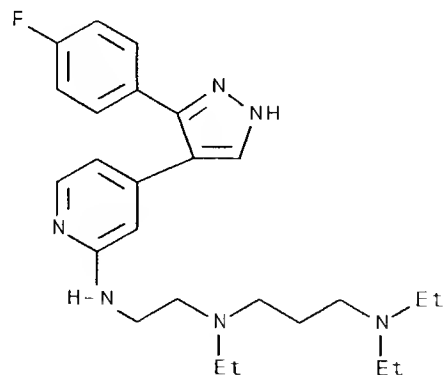
372

**Example A-346**

5           N-[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]-4-methyl-1-piperazinepropanamine (2E)-2-butenedioate (1:1)

**Example A-347**

10           3-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]-1,2-propanediol;

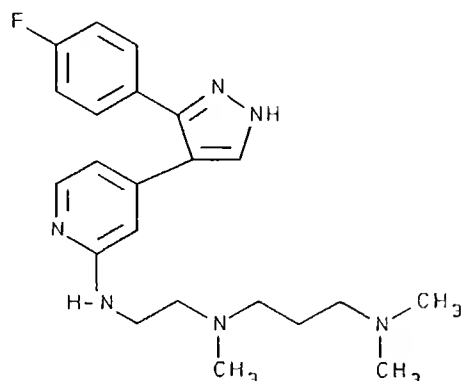
**Example A-348**

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373

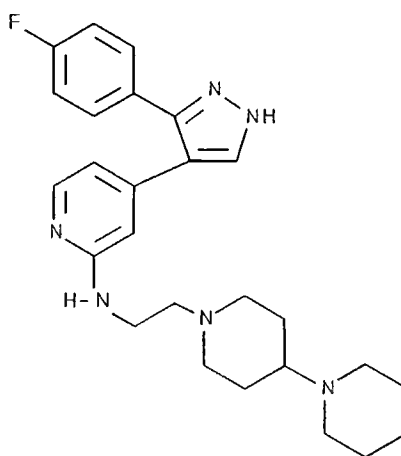
N,N,N'-triethyl-N'-[2-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]ethyl]-1,3-propanediamine;

5

**Example A-349**

N-[2-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]ethyl]-N,N',N'-trimethyl-1,3-propanediamine;

10

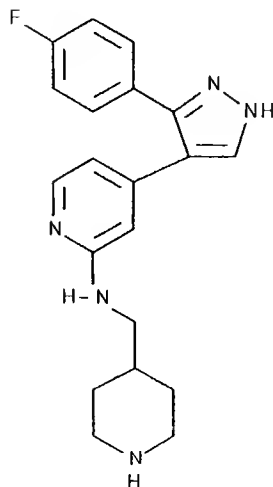
**Example A-350**

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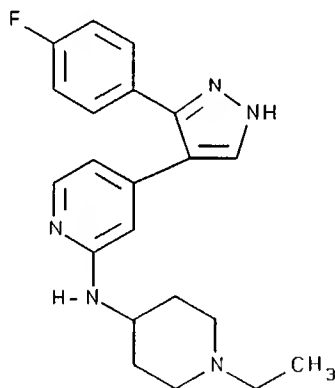
N-(2-[1,4'-bipiperidin]-1'-ylethyl)-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinamine;

20

374

**Example A-351**

5            4 - [3 - (4 - fluorophenyl) - 1H - pyrazol - 4 - yl] - N - (4 -  
piperidinylmethyl) - 2 - pyridinamine;

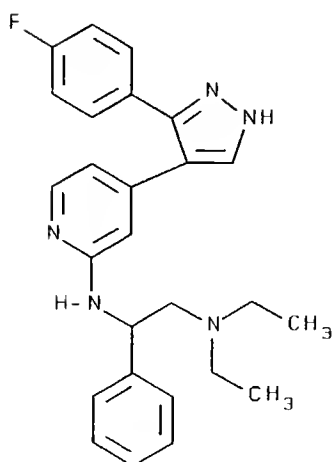
**Example A-352**

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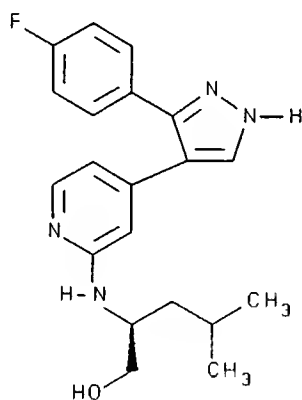
N - (1 - ethyl - 4 - piperidinyl) - 4 - [3 - (4 - fluorophenyl) - 1H -  
pyrazol - 4 - yl] - 2 - pyridinamine;

15

375

**Example A-353**

5           N2,N2-diethyl-N1-[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]-1-phenyl-1,2-ethanediamine;

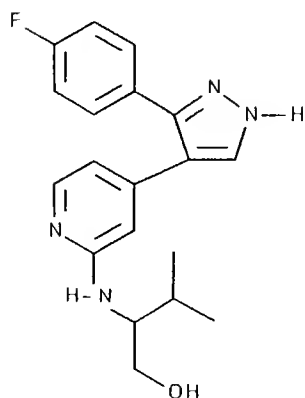
**Example A-354**

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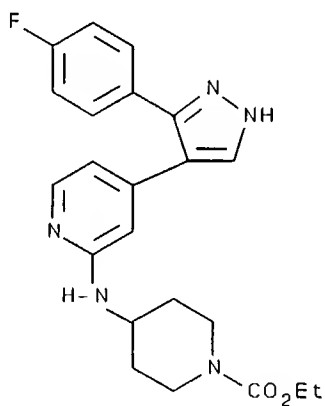
(2S)-2-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]-4-methyl-1-pentanol;

15

376

**Example A-355**

5            2-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]-3-methyl-1-butanol;

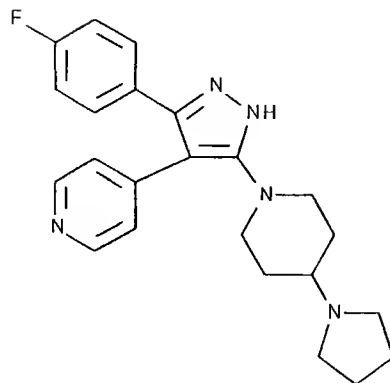
**Example A-356**

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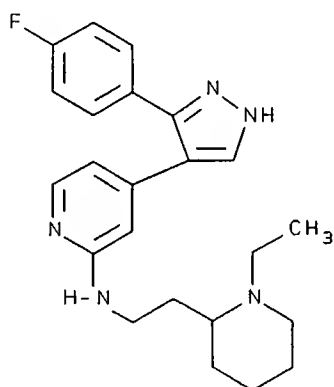
          ethyl 4-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]-1-piperidinecarboxylate;

15

377

**Example A-357**

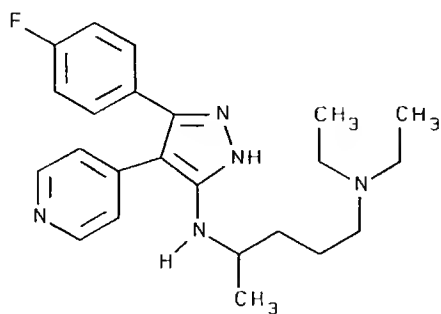
5            4-[3-(4-fluorophenyl)-5-(4-(1-pyrrolidinyl)-1-piperidinyl)-1H-pyrazol-4-yl]pyridine, trihydrochloride;

**Example A-358**

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N-[2-(1-ethyl-2-piperidinyl)ethyl]-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinamine;

15

**Example A-359**

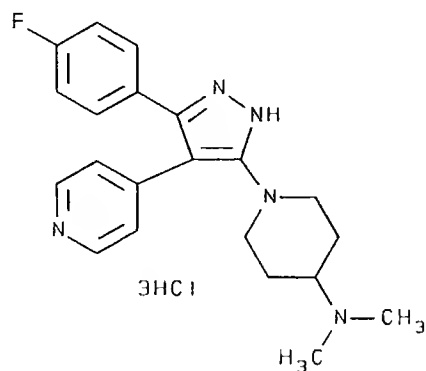


378

N1,N1,-diethyl-N4-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1,4-pentanediamine;

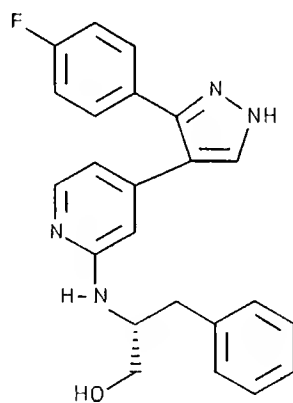
**Example A-360**

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1-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-N,N-dimethyl-4-piperidinamine, trihydrochloride;

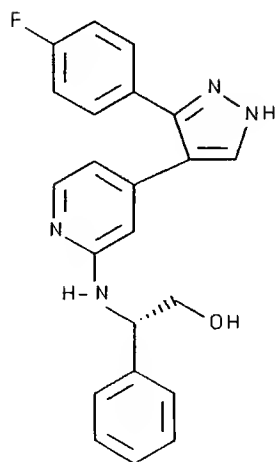
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**Example A-361**

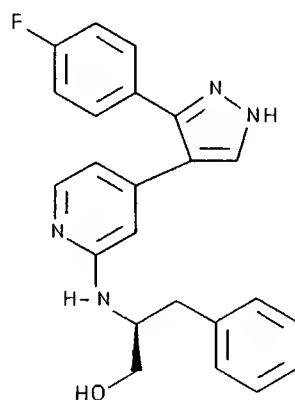
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( $\beta$ R)- $\beta$ -[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]benzene propanol;

379

**Example A-362**

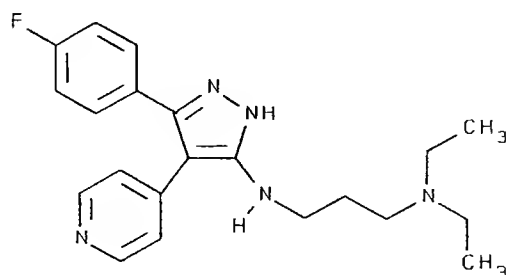
5           (βS)-β-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]benzene ethanol;

**Example A-363**

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          (βS)-β-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]benzene propanol;

15

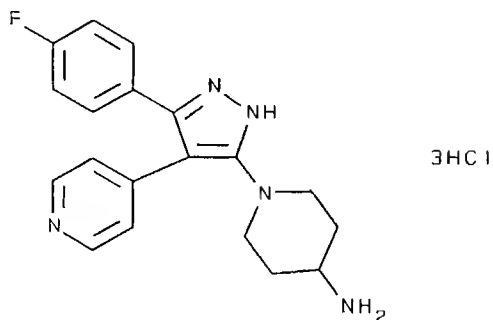
**Example A-364**

380

N,N-diethyl-N'-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1,3-propanediamine;

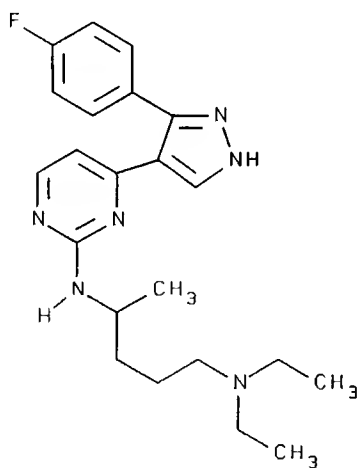
**Example A-365**

5



1-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-piperidinamine, trihydrochloride;

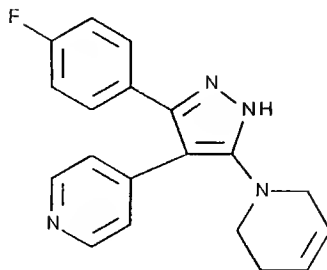
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**Example A-366**

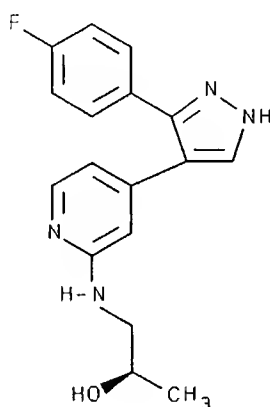
N1,N1-diethyl-N4-[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyrimidinyl]-1,4-pentanediamine;

15

381

**Example A-367**

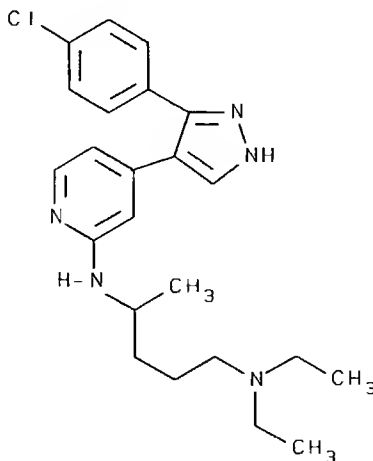
5            1-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1,2,3,6-hexahydropyridine;

**Example A-368**

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(2R)-1-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]-2-propanol;

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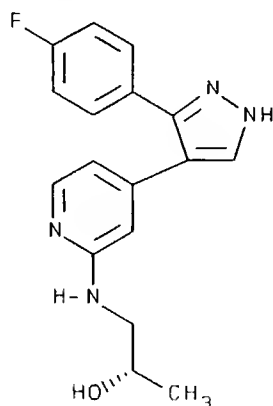
**Example A-369**

382

N4-[4-[3-(4-chlorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]-N1,N1-diethyl-1,4-pentanediamine;

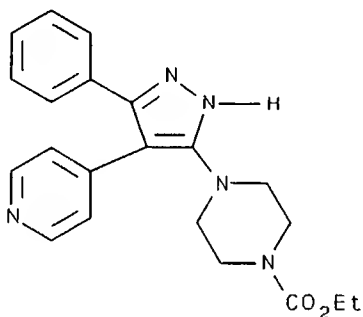
**Example A-370**

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(2S)-1-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]-2-propanol;

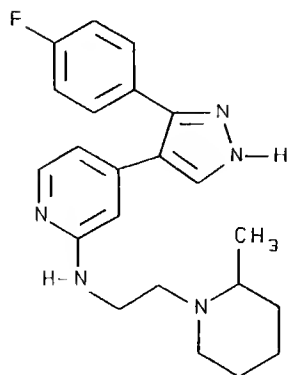
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**Example A-371**

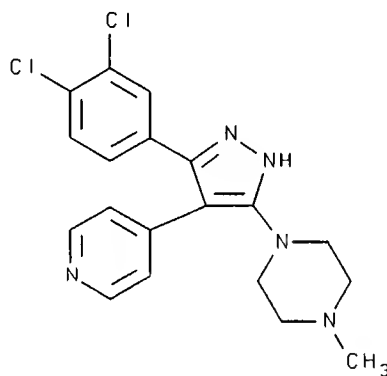
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ethyl 4-[5-phenyl-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1-piperazinecarboxylate;

383

**Example A-372**

5            4 - [3 - (4 - fluorophenyl) - 1H - pyrazol - 4 - yl] - N - [3 - (2 - methyl - 1 - piperidinyl) propyl] - 2 - pyridinamine;

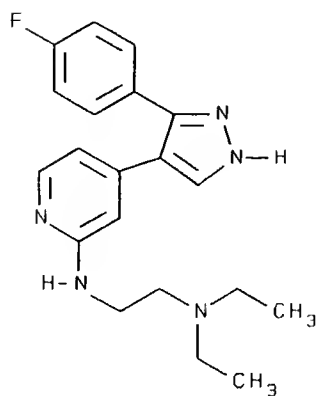
**Example A-373**

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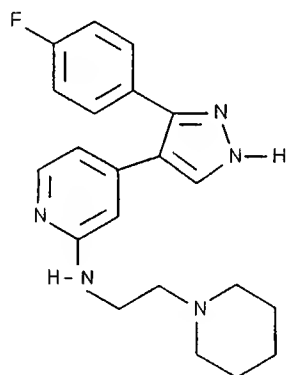
1 - [5 - (3,4 - dichlorophenyl) - 4 - (4 - pyridinyl) - 1H - pyrazol - 3 - yl] - 4 - methylpiperazine;

15

384

**Example A-374**

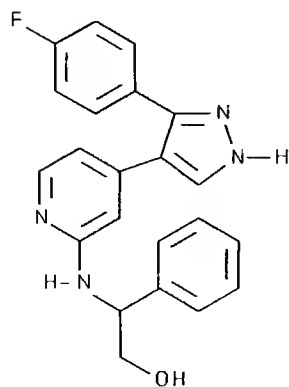
5           N,N-diethyl-N' - [4 - [3 - (4-fluorophenyl) - 1H-pyrazol - 4 -  
yl] - 2-pyridinyl] - 1,2-ethanediamine;

**Example A-375**

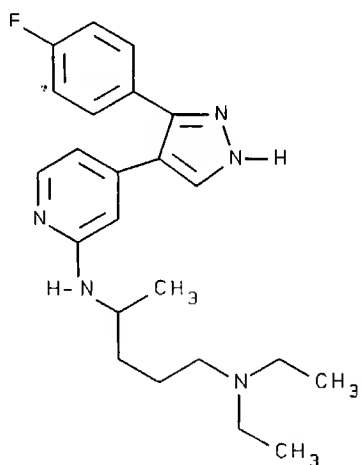
10           4 - [3 - (4-fluorophenyl) - 1H-pyrazol - 4 - yl] - N - [2 - (1 -  
piperidinyl) ethyl] - 2-pyridinamine;

15

385

**Example A-376**

5           (βR)-β-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]benzene ethanol;

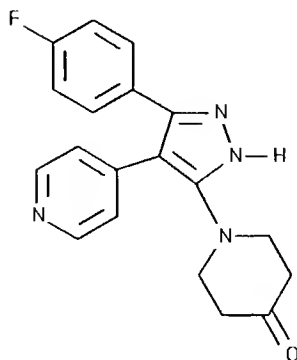
**Example A-377**

10

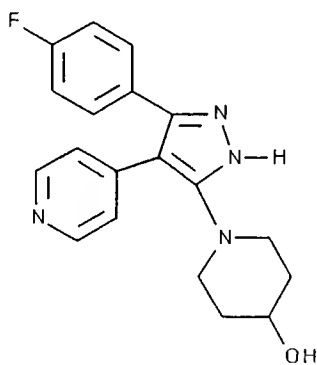
N1,N1-diethyl-N4-[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]-1,4-pentanediamine;



386

**Example A-378**

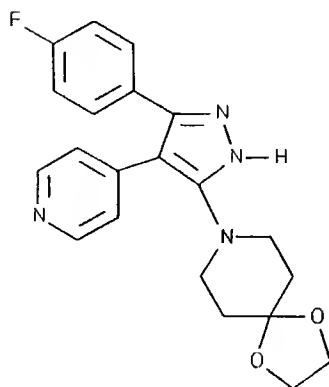
5            1 - [5 - (4-fluorophenyl) - 4 - (4-pyridinyl) - 1H-pyrazol - 3 -  
yl] - 4-piperidinone;

**Example A-379**

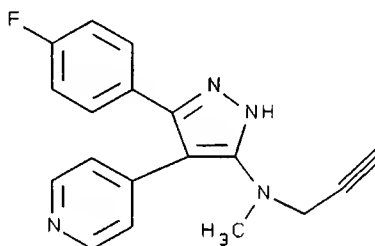
10

1 - [5 - (4-fluorophenyl) - 4 - (4-pyridinyl) - 1H-pyrazol - 3 -  
yl] - 4-piperidinol;

387

**Example A-380**

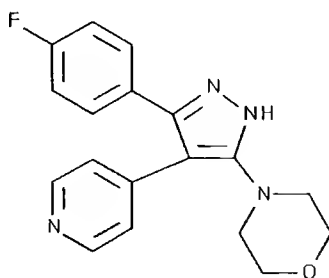
5            8-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1,4-dioxo-8-azaspiro[4.5]decane;

**Example A-381**

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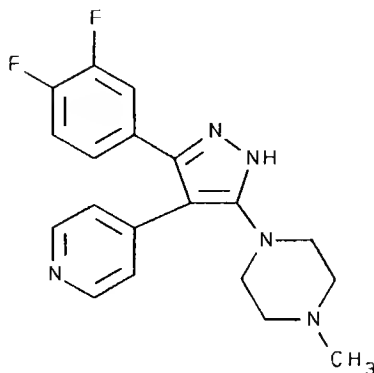
          5-(4-fluorophenyl)-N-methyl-N-2-propynyl-4-(4-pyridinyl)-1H-pyrazol-3-amine;

15

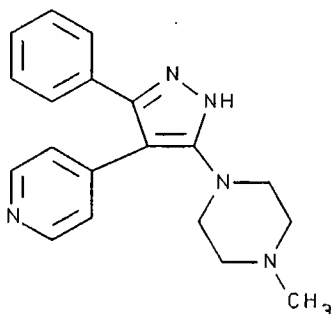
**Example A-382**

20            4-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]morpholine;

388

**Example A-383**

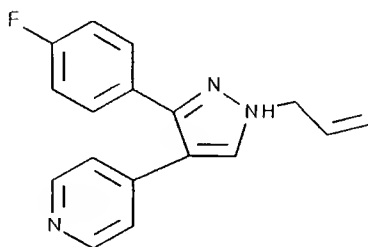
5            1-[5-(3,4-difluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-methylpiperazine;

**Example A-384**

10

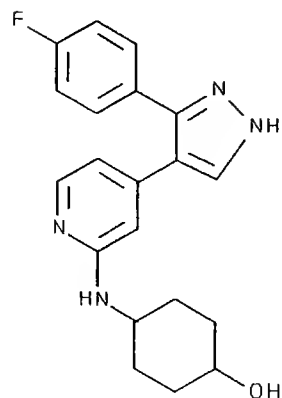
1-methyl-4-[5-phenyl-4-(4-pyridinyl)-1H-pyrazol-3-yl]piperazine;

15

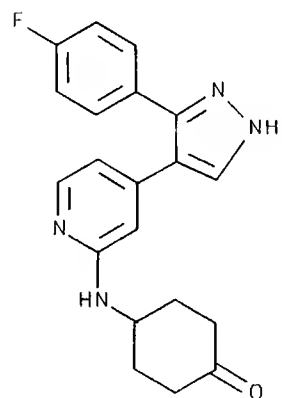
**Example A-385**

20            4-[3-(4-fluorophenyl)-1-(2-propenyl)-1H-pyrazol-4-yl]pyridine, monohydrochloride;

389

**Example A-386**

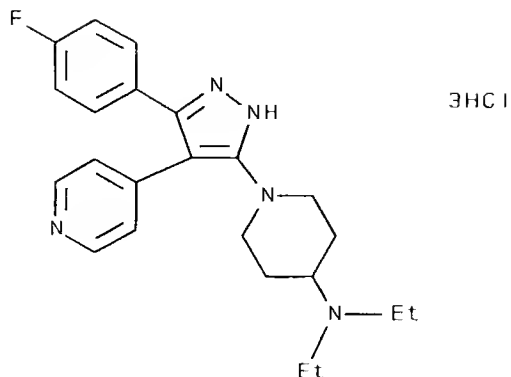
5           trans-4-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]cyclohexanol;

**Example A-387**

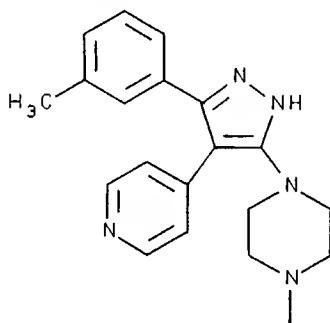
10

4-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]cyclohexanone;

390

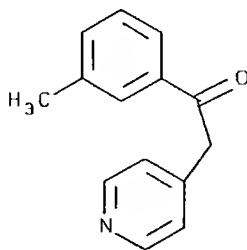
**Example A-388**

5            1-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-N,N-diethyl-4-piperidinamine, trihydrochloride;

**Example A-389**

10            1-[5-(3-tolyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-methylpiperazine:

15    Step 1. Preparation of 1-tolyl-2-(4-pyridyl)ethanone

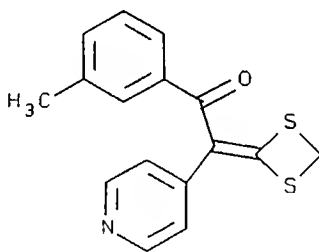


20            Methyl 3-methylbenzoate (6.0 g, 40 mmol),  
tetrahydrofuran (50 mL), and 4-picoline (4.1 g, 44 mmol)  
were stirred at -78 °C under an atmosphere of nitrogen.

391

Sodium (bis)trimethylsilylamide 1.0 M in tetrahydrofuran (88 mL, 88 mmol) was added dropwise. The mixture was allowed to warm to room temperature, stirred for 16 hours and then was poured into saturated aqueous sodium bicarbonate solution. The mixture was then extracted with ethyl acetate (3 X 50 mL). The combined organics were washed with brine (2 X 50 mL), dried over magnesium sulfate, and concentrated. The product was recrystallized from ethyl acetate/hexane to yield a light yellow solid (5.7 g, 67%), mp 118.0-119.0 °C; <sup>1</sup>H NMR (acetone-d<sub>6</sub>/300 MHz) 8.50 (m, 2H), 7.90 (m, 2H), 7.44 (m, 2H), 7.29 (m, 2H), 4.45 (s, 2H), 2.41 (s, 3H); ESHRMS m/z 212.1067 (M+H, C<sub>14</sub>H<sub>13</sub>NO requires 212.1075); Anal. Calc'd for C<sub>14</sub>H<sub>13</sub>NO: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.54; H, 6.30; N, 6.56.

Step 2. Preparation of 1-(3-tolyl)-2-(1,3-dithietan-2-ylidene)-2-(4-pyridyl)ethanone



20

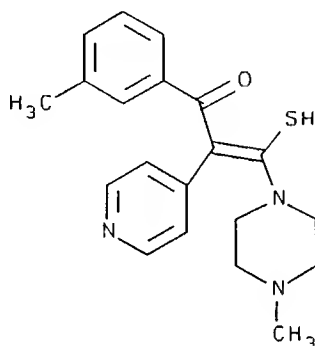
1-tolyl-2-(4-pyridyl)ethanone (4.22 g, 20 mmol), acetone (100 mL), potassium carbonate (8.3 g, 60 mmol), carbon disulfide 4.56 g, 60 mmol), and dibromomethane (10.43 g, 60 mmol) were stirred at room temperature for 16 hours. Water (100 mL) was added and the mixture was extracted with ethyl acetate (3 X 50 mL). The combined organic extracts were washed with brine (2 X 50 mL), dried over magnesium sulfate and concentrated. This crude material was purified by either flash column chromatography eluting with ethyl acetate:hexane or crystallization from ethyl acetate/hexane to yield a

30

392

yellow solid (4.8 g, 80%), mp 178.6-179.2 °C; <sup>1</sup>H NMR (acetone-d<sub>6</sub>/300 MHz) 8.47 (m, 2H), 7.08 (m, 6H), 4.37 (s, 2H), 2.21 (s, 3H); ESHRMS *m/z* 300.0521 (M+H, C<sub>16</sub>H<sub>13</sub>NOS<sub>2</sub> requires 300.0517); Anal. Calc'd for C<sub>16</sub>H<sub>13</sub>NOS<sub>2</sub>: C, 64.18; H, 4.38; N, 4.68. Found: C, 64.08; H, 4.25; N, 4.62.

Step 3. Preparation of 1-[3-(3-tolyl)-3-oxo-2-(4-pyridinyl)-1-thiopropyl]-4-methylpiperazine



10

The dithietane compound from step 2 above (3.0 g, 10 mmol), N-methylpiperazine (5.0 g, 50 mmol), and toluene (50 mL) were refluxed using a Dean-Stark apparatus for one to three hours. The reaction was allowed to cool to room temperature and was concentrated to dryness under high vacuum. This thick, oily material was crystallized from ethyl acetate / hexane (2.9 g, 82%), mp 124.8-125.8 °C; <sup>1</sup>H NMR (acetone-d<sub>6</sub>/300 MHz) 8.57 (m, 2H), 7.75 (m, 2H), 7.54 (m, 2H), 7.37 (m, 2H) 6.54 (s, 1H), 4.27 (m, 2H), 4.19 (m, 1H), 3.83 (m, 1H), 2.47-2.28 (m, 6H), 2.22 (s, 3H), 2.17 (m, 1H); ESHRMS *m/z* 354.1669 (M+H, C<sub>20</sub>H<sub>23</sub>N<sub>3</sub>OS requires 354.1640); Anal. Calc'd for C<sub>20</sub>H<sub>23</sub>N<sub>3</sub>OS: C, 67.96; H, 6.56; N, 11.89. Found: C, 67.79; H, 6.66; N, 11.88.

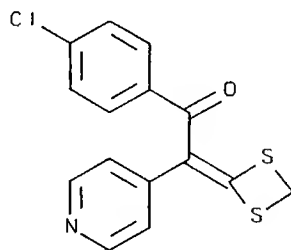
20

Step 4. Preparation of 1-[5-(3-tolyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-methylpiperazine.

The thioamide compound from step 3 above (1.06 g, 3 mmol), tetrahydrofuran (50 mL), and hydrazine (15 mL, 15 mmol, 1.0 M) in tetrahydrofuran were stirred at room temperature for 16 hours. A white solid was collected by filtration. Purification when necessary was by trituration or recrystallization (0.98 g, 97%), mp 261.9-262.0 °C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>/300 MHz) 12.6 (brs, 1H), 8.42 (m, 2H), 7.2 (m, 4H), 7.12 (s, 1H), 7.0 (m, 1H), 2.86 (m, 4H), 2.34 (m, 4H) 2.25 (s, 3H), 2.16 (s, 3H); ESHRMS m/z 334.2049 (M+H, C<sub>20</sub>H<sub>23</sub>N<sub>5</sub> requires 334.2032); Anal. Calc'd for C<sub>20</sub>H<sub>23</sub>N<sub>5</sub>: C, 72.04; H, 6.95; N, 21.00. Found: C, 71.83; H, 7.06; N, 20.83.

Additional dithietanes and pyrazoles that were synthesized by selection of the corresponding starting reagents in accordance with the chemistry described in Scheme XXI and further illustrated in Example 389 above include compounds A-390 through A-426 disclosed below.

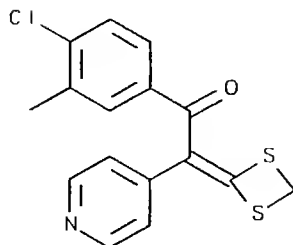
**Example A-390**



mp 185.3-185.4 °C; <sup>1</sup>H NMR (acetone-d<sub>6</sub>/300 MHz) 8.49 (m, 2H), 7.31 (m, 4H), 7.09 (m, 2H), 4.39 (s, 2H); ESHRMS m/z 319.9981 (M+H, C<sub>15</sub>H<sub>10</sub>ClNOS<sub>2</sub> requires 319.9971); Anal. Calc'd for C<sub>15</sub>H<sub>10</sub>ClNOS<sub>2</sub>: C, 56.33; H, 3.15; N, 4.38. Found: C, 56.47; H, 3.13; N, 4.44.

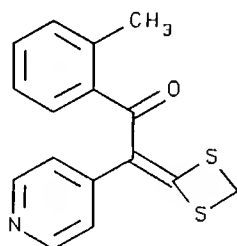


394

**Example A-391**

5           1-(4-chloro-3-methylphenyl)-2-1,3-dithietan-2-ylidene-2-pyridin-4-yl-ethanone

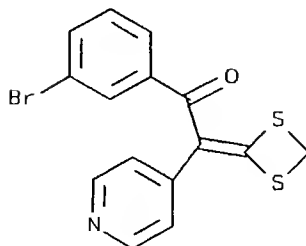
mp 164.0-165.0 °C; <sup>1</sup>H NMR (acetone-d<sub>6</sub>/300 MHz) 8.49 (m, 2H), 7.25 (m, 2H), 7.0 (m, 3H), 4.38 (s, 2H), 2.24 (s, 3H); ESHRMS *m/z* 334.0130 (M+H, C<sub>16</sub>H<sub>12</sub>ClNOS<sub>2</sub> requires 334.0127); Anal. Calc'd for C<sub>16</sub>H<sub>12</sub>ClNOS<sub>2</sub>: C, 57.56; H, 3.62; N, 4.20. Found: C, 57.68; H, 3.67; N, 4.17.

**Example A-392**

15           mp 126.5-126.6 °C; <sup>1</sup>H NMR (acetone-d<sub>6</sub>/300 MHz) 8.40 (m, 2H), 7.17 (m, 2H), 7.0 (m, 4H), 4.39 (s, 2H), 2.85 (s, 3H); ESHRMS *m/z* 300.0483 (M+H, C<sub>16</sub>H<sub>13</sub>NOS<sub>2</sub> requires 300.0517); Anal. Calc'd for C<sub>16</sub>H<sub>13</sub>NOS<sub>2</sub>: C, 64.18; H, 4.38; N, 4.68. Found: C, 64.05; H, 4.27; N, 4.59.

395

## Example A-393

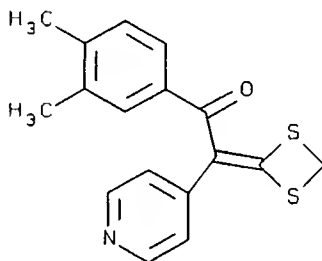


5

mp 159.6-159.7 °C; <sup>1</sup>H NMR (acetone-d<sub>6</sub>/300 MHz) 8.52 (m, 2H), 7.6 (m, 1H), 7.50 (s, 1H), 7.21 (m, 2H), 7.13 (m, 2H), 4.40 (s, 2H); ESHRMS *m/z* 363.9503 (M+H, C<sub>15</sub>H<sub>10</sub>BrNOS<sub>2</sub> requires 363.9465); Anal. Calc'd for C<sub>15</sub>H<sub>10</sub>BrNOS<sub>2</sub>: C, 49.46; H, 2.77; N, 3.84. Found: C, 49.51; H, 2.68; N, 3.74.

10

## Example A-394

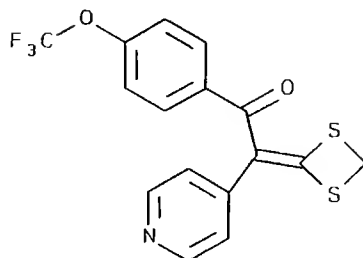


15

mp 198.8-198.9 °C; <sup>1</sup>H NMR (acetone-d<sub>6</sub>/300 MHz) 8.45 (m, 2H), 7.05 (m, 3H), 6.95 (m, 1H), 6.82 (m, 1H), 4.29 (s, 2H), 2.14 (s, 3H), 2.08 (s, 3H); ESHRMS *m/z* 314.0691 (M+H, C<sub>17</sub>H<sub>15</sub>NOS<sub>2</sub> requires 314.0673).

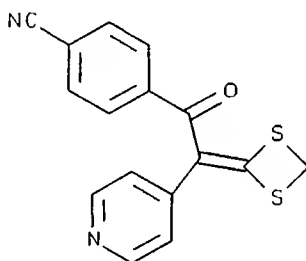
20

396

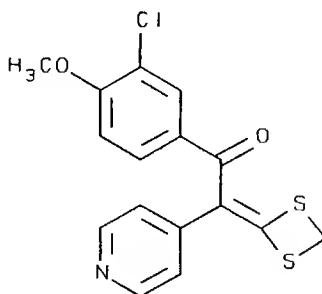
**Example A-395**

5 mp 182.6-183.0 °C.  $^1\text{H}$  NMR (acetone- $d_6$ /300 MHz) 8.50 (m, 2H), 7.42 (d, 2H,  $J = 8.5$  Hz), 7.23 (d, 2H,  $J = 8.5$  Hz), 7.10 (m, 2H), 4.40 (s, 2H). ESHRMS  $m/z$  370.0173 (M+H,  $\text{C}_{16}\text{H}_{10}\text{F}_3\text{NO}_2\text{S}_2$  requires 370.0183).

10

**Example A-396**

15 mp 193.3-193.4 °C.  $^1\text{H}$  NMR (acetone- $d_6$ /300 MHz) 8.49 (m, 2H), 7.69 (d, 2H,  $J = 8.2$  Hz), 7.46 (d, 2H,  $J = 8.2$  Hz), 7.01 (m, 2H), 4.43 (s, 2H). ESHRMS  $m/z$  311.0327 (M+H,  $\text{C}_{16}\text{H}_{10}\text{N}_2\text{O}_2\text{S}_2$  requires 311.0313).

**Example A-397**

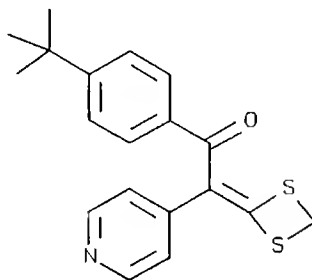
20

397

mp 191.5-192.5 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>/ 300 MHz) 8.55 (dd, 2H, *J* = 4.6, 1.6 Hz), 7.4 (m, 1H), 7.09-7.03 (m, 3H), 6.67 (d, 1H, *J* = 8.7 Hz), 4.17 (s, 2H), 3.86 (s, 3H); ESHRMS *m/z* 350.0090 (M+H, C<sub>16</sub>H<sub>12</sub>ClNO<sub>2</sub>S<sub>2</sub> requires 350.0076);  
5 Anal. Calc'd. for C<sub>16</sub>H<sub>12</sub>ClNO<sub>2</sub>S<sub>2</sub>: C, 54.93; H, 3.60; N, 4.00; Cl, 10.13; S, 18.33. Found: C, 54.74; H, 3.60; N, 3.89; Cl, 10.45; S, 18.32.

## Example A-398

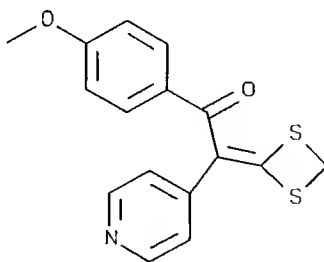
10



mp 172.1-173.1 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub> / 300 MHz) 8.51 (dd, 2H, *J* = 4.4, 1.6 Hz), 7.23-7.21 (m, 4H), 7.04 (dd, 2H, *J* = 4.6, 1.6 Hz), 4.17 (s, 2H), 1.25 (s, 9H); ESHRMS  
15 *m/z* 342.1004 (M+H, C<sub>19</sub>H<sub>19</sub>NOS<sub>2</sub> requires 342.0986); Anal. Calc'd for C<sub>19</sub>H<sub>19</sub>NOS<sub>2</sub>: C, 66.83; H, 5.61; N, 4.10; S, 18.78. Found: C, 66.97; H, 5.89; N, 4.02; S, 18.64.

## Example A-399

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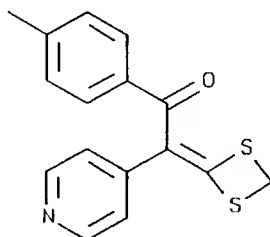


mp 203.0-204.1 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub> / 300 MHz) 8.52 (dd, 2H, *J* = 4.4, 1.6 Hz), 7.29 (d, 1H, *J* = 6.8 Hz), 7.28 (d, 1H, *J* = 7.0 Hz), 7.05 (dd, 2H, *J* = 4.4, 1.6 Hz), 6.70 (d, 1H, *J* = 6.8 Hz), 6.69 (d, 1H, *J* = 6.8 Hz), 4.17 (s, 2H), 3.79 (s, 3H); ESHRMS *m/z* 316.0475 (M+H, C<sub>16</sub>H<sub>13</sub>NO<sub>2</sub>S<sub>2</sub>  
25

398

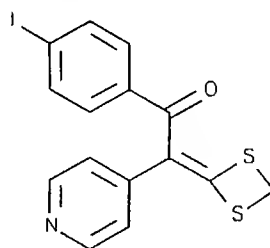
requires 316.0466); Anal. Calc'd. for  $C_{16}H_{13}NO_2S_2$ : C, 60.93; H, 4.15; N, 4.44; S, 20.33. Found: C, 60.46; H, 4.17; N, 4.37; S, 19.84.

5

**Example A-400**

mp 209.1-215.1 °C;  $^1H$  NMR ( $CDCl_3$  / 300 MHz) 8.50 (dd, 2H,  $J = 4.4, 1.6$  Hz), 7.20 (d, 2H,  $J = 8.0$  Hz), 7.03-6.99 (m, 4H), 4.18 (s, 2H), 2.30 (s, 3H); ESHRMS  $m/z$  300.0517 ( $M+H$ ,  $C_{16}H_{13}NOS_2$  requires 300.0517); Anal. Calc'd. for  $C_{16}H_{13}NOS_2$ : C 64.18; H, 4.38; N, 4.69; S, 21.42. Found: C, 64.02; H, 4.62; N, 4.54; S, 21.24.

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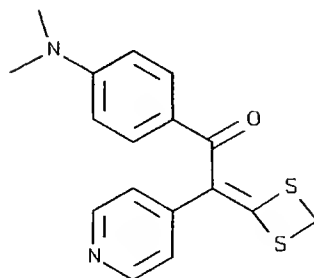
**Example A-401**

mp 257.6-257.7 °C;  $^1H$  NMR ( $CDCl_3$  / 300 MHz) 8.51 (dd, 2H,  $J = 4.4, 1.6$  Hz), 7.57 (d, 2H,  $J = 8.5$  Hz), 7.27-6.99 (m, 4H), 4.18 (s, 2H); ESHRMS  $m/z$  411.9348 ( $M+H$ ,  $C_{15}H_{10}NIO_2S_2$  requires 411.9327); Anal. Calc'd. for  $C_{15}H_{10}NIO_2S_2$ : C, 43.81; H, 2.45; N, 3.41. Found: C, 43.71; H, 2.27; N, 3.41.

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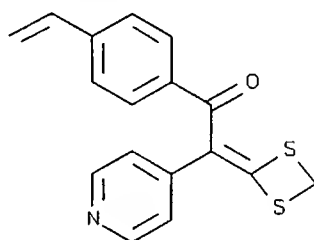
399

## Example A-402



5 mp 197.3-202.2 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub> / 300 MHz) 8.53 (dd, 2H, *J* = 4.4, 1.6 Hz), 7.26 (d, 2H, *J* = 9.3 Hz), 7.09 (dd, 2H, *J* = 4.4, 1.6 Hz), 6.43 (d, 2H, *J* = 9.3 Hz), 4.14 (s, 2H), 2.97 (s, 6H); ESHRMS *m/z* 329.0789 (M+H, C<sub>17</sub>H<sub>16</sub>N<sub>2</sub>OS<sub>2</sub> requires 329.0782); Anal. Calc'd. for C<sub>17</sub>H<sub>16</sub>N<sub>2</sub>OS<sub>2</sub>: C, 62.17; H, 4.91; N, 8.53; S, 19.53. Found: C, 61.93; H, 5.12; N, 8.46; S, 19.26.

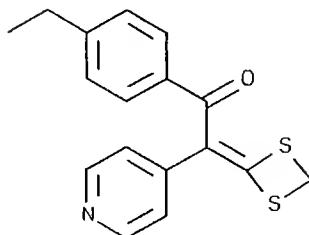
## Example A-403



15 mp 176.6-176.7 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub> / 300 MHz) 8.51 (dd, 2H, *J* = 4.4, 1.6 Hz), 7.29-7.22 (m, 4H), 7.03 (dd, 2H, *J* = 4.4, 1.6 Hz), 6.64 (dd, 1H, *J* = 17.5, 10.9 Hz), 5.76 (d, 1H, *J* = 17.7 Hz), 5.31 (d, 1H, *J* = 10.9 Hz), 4.19 (s, 2H); ESHRMS 312.0513 (M+H, C<sub>17</sub>H<sub>13</sub>NOS<sub>2</sub> requires 312.0517); Anal. Calc'd. for C<sub>17</sub>H<sub>13</sub>NOS<sub>2</sub>: C, 65.56; H, 4.21; N, 4.50. Found: C, 65.75; H, 4.11; N, 4.46.

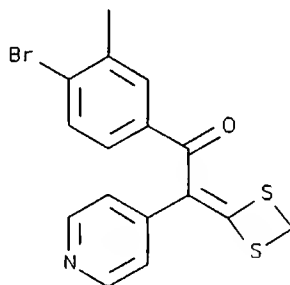
400

## Example A-404



5 mp 174.8-175.0 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$  / 300 MHz) 8.50 (dd, 2H,  $J = 4.4, 1.6$  Hz), 7.23-7.20 (m, 4H), 7.03 (dd, 2H,  $J = 4.6, 1.6$  Hz), 4.17 (s, 2H), 2.59 (q, 2H,  $J = 7.6$  Hz), 1.17 (t, 3H,  $J = 7.7$  Hz); ESHRMS  $m/z$  314.0677 ( $\text{M}+\text{H}$ ,  $\text{C}_{17}\text{H}_{15}\text{NOS}_2$  requires 314.0673); Anal. Calc'd. for  
10  $\text{C}_{17}\text{H}_{15}\text{NOS}_2$ : C, 65.14; H, 4.82; N, 4.47. Found: C, 64.90; H, 4.62; N, 4.45.

## Example A-405



15 mp 167.1-167.5 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$  / 300 MHz) 8.52 (dd, 1H,  $J = 4.4, 1.6$  Hz), 7.33 (d, 1H,  $J = 8.3$  Hz), 7.02-7.00 (m, 3H), 6.87-6.83 (m, 1H), 4.19 (s, 2H), 2.28 (s, 3H); ESHRMS  $m/z$  379.9577 ( $\text{M}+\text{H}$ ,  $\text{C}_{16}\text{H}_{12}\text{BrNOS}_2$  requires 379.9622); Anal. Calc'd. for  $\text{C}_{16}\text{H}_{12}\text{BrNOS}_2$ : C, 50.80; H, 3.20; N, 3.70. Found: C, 50.69; H, 3.19; N, 3.71.